Supplementary Information

Synthesis of new piperazinyl-pyrrolo[1,2-*a*]quinoxaline derivatives as inhibitors of *Candida albicans* multidrug transporters by a Buchwald-Hartwig cross-coupling reaction

Jean Guillon,[a]‡ Shweta Nim, ‡[b] Stéphane Moreau,[a] Luisa Ronga,[a] Solène Savrimoutou,[a] Elisabeth Thivet,[a] Mathieu Marchivie,[c] Attilio Di Pietro,[d] Rajendra Prasad[e] and Marc Le Borgne*[f]

[a]*Univ. Bordeaux, INSERM U1212 – UMR CNRS 5320, ARNA Laboratory, UFR des Sciences Pharmaceutiques, F-33076 Bordeaux cedex, France*

[b]*School of Life Sciences, Jawaharlal Nehru University, 110067 New Delhi, India*

[c]*CNRS, Univ. Bordeaux, Bordeaux INP, ICMCB, UMR 5026, F-33608 Pessac cedex, France*

[d]*DRMP group, IBCP, UMR 5086 (MMSB), CNRS/Lyon I University, 69367 Lyon, France*

[e]*Amity Institute of Integrative Sciences and Health, AMITY University, Education Valley, Gurgaon 122413, India*

[f]*Université de Lyon, Université Claude Bernard Lyon 1, Faculté de Pharmacie - ISPB, EA 4446 Bioactive Molecules and Medicinal Chemistry, SFR Santé Lyon-Est CNRS UMS3453 - INSERM US7, Lyon, France. E-mail:* marc.le-borgne@univ-lyon1.fr

‡ These authors contributed equally to this work.

† Electronic supplementary information (ESI) available. See DOI: 10.1039/xxxxxxxxxx

Table of Contents

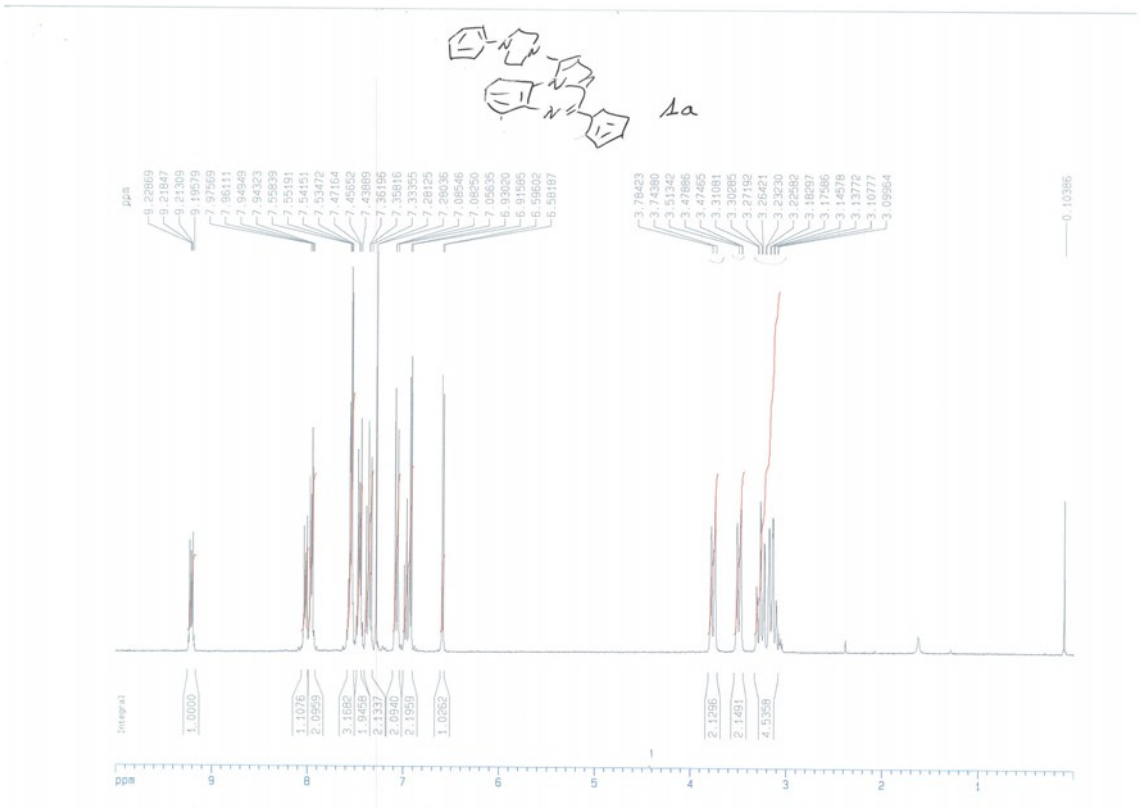

Fig. S1. ^{1}H NMR spectrum of **1a**.

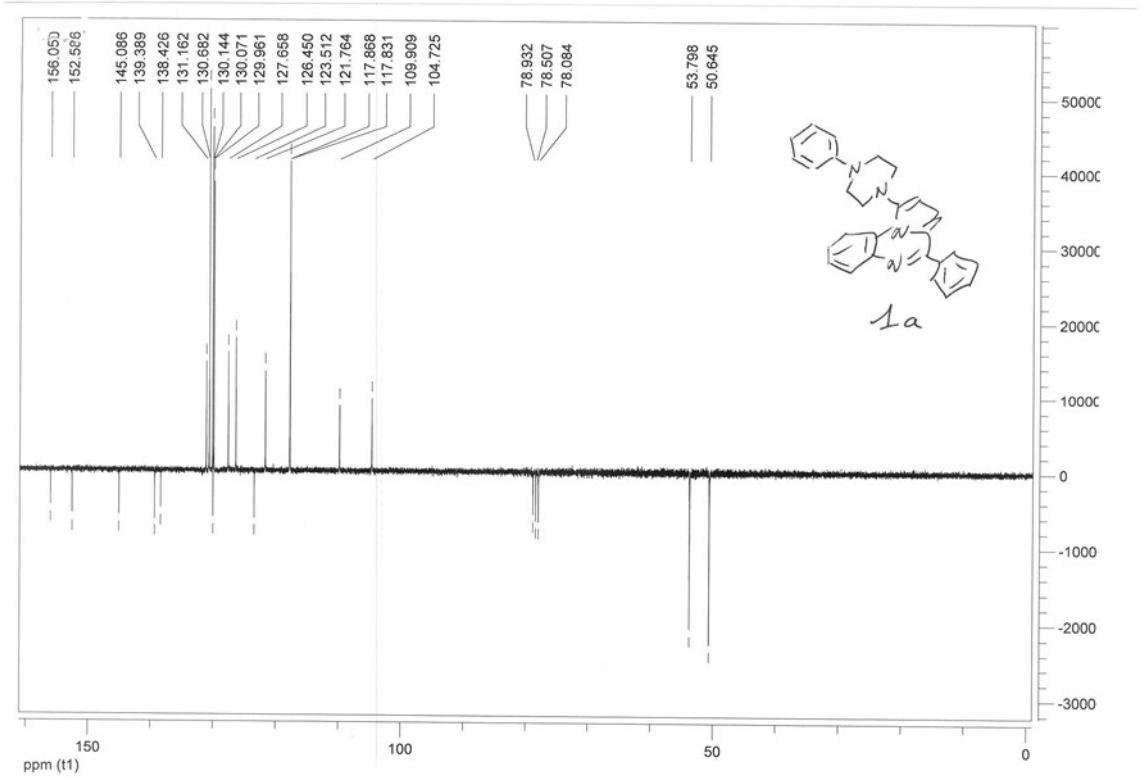

Fig. S2. ^{13}C NMR spectrum of **1a**.

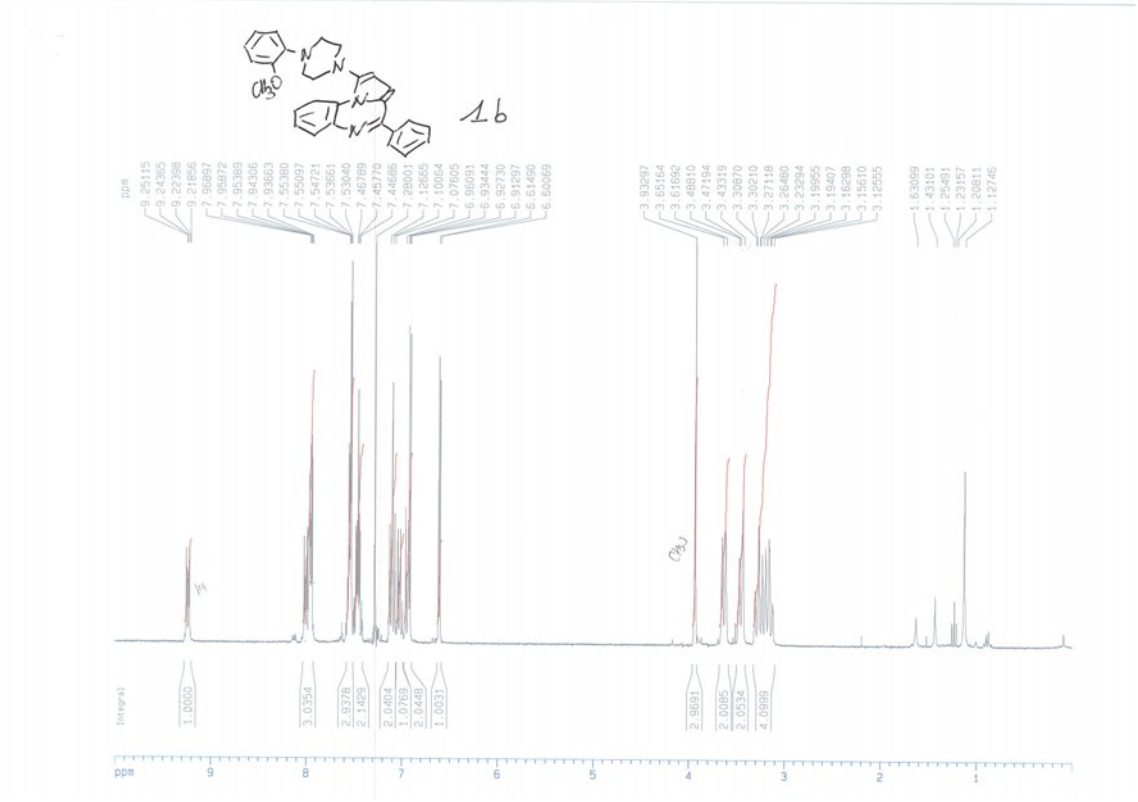

Fig. S3. ^{1}H NMR spectrum of **1b**.

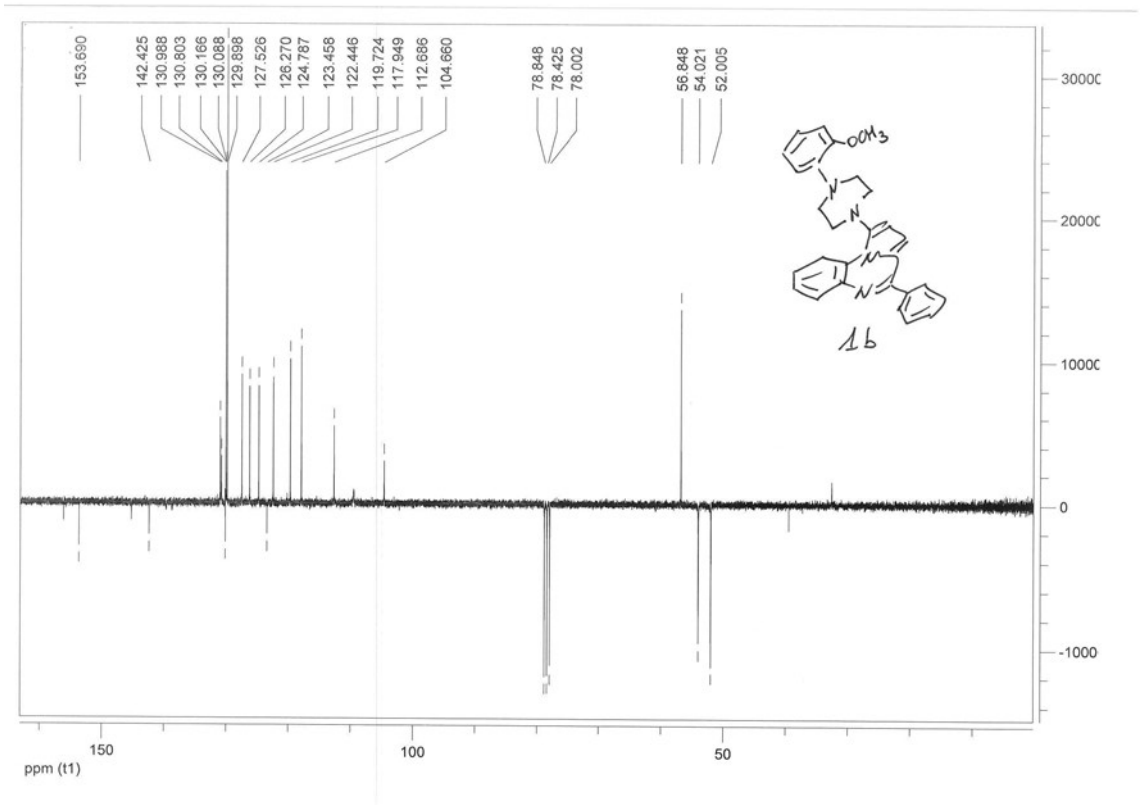

Fig. S4. ^{13}C NMR spectrum of **1b**.

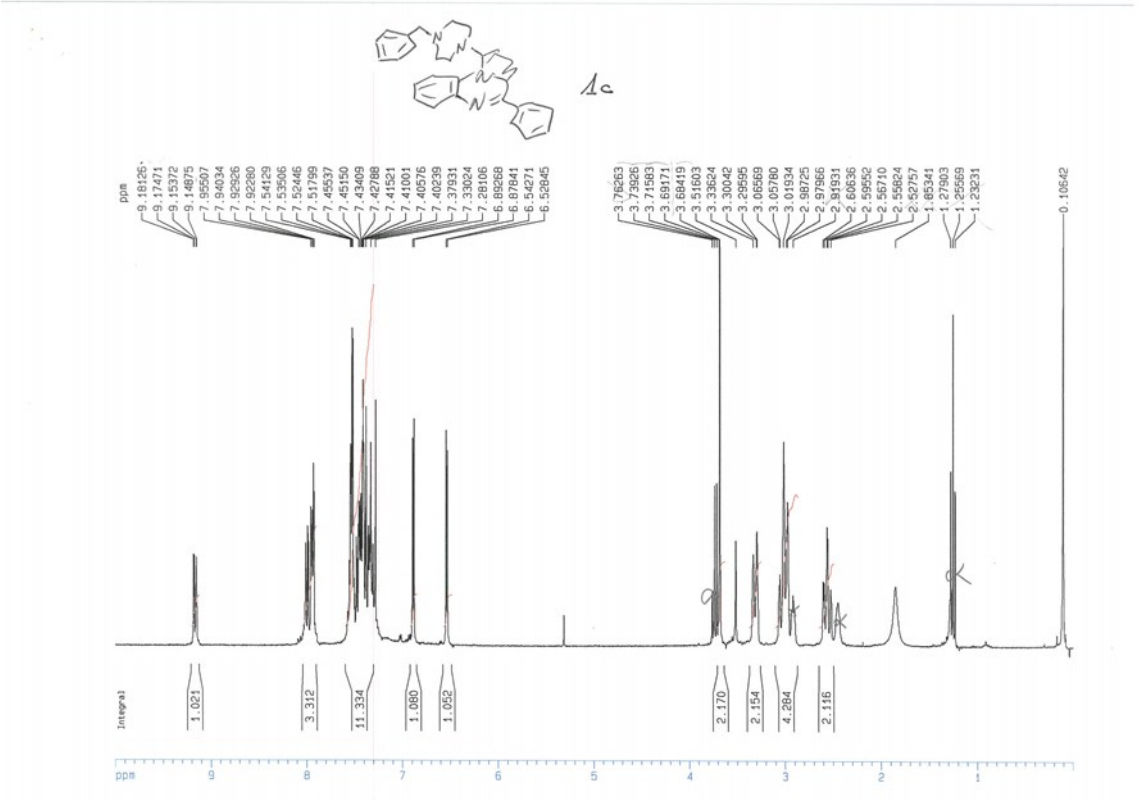

Fig. S5. ^{1}H NMR spectrum of **1c**.

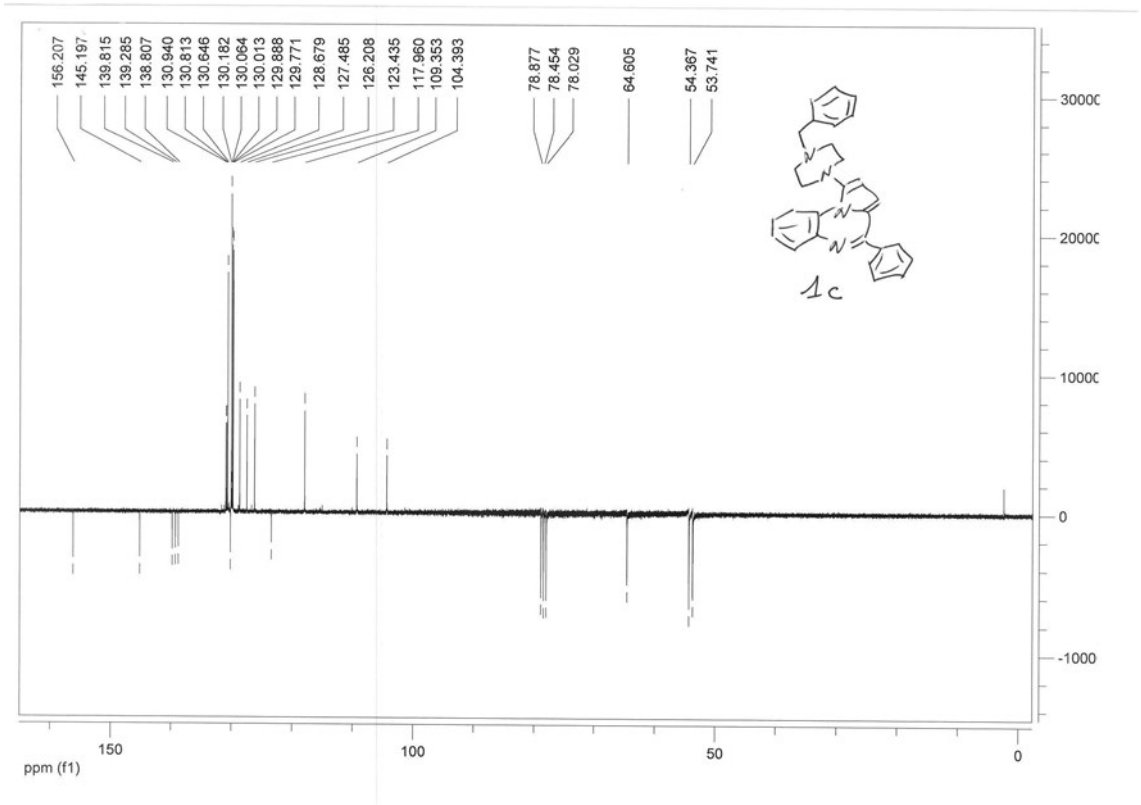

Fig. S6. ^{13}C NMR spectrum of **1c**.

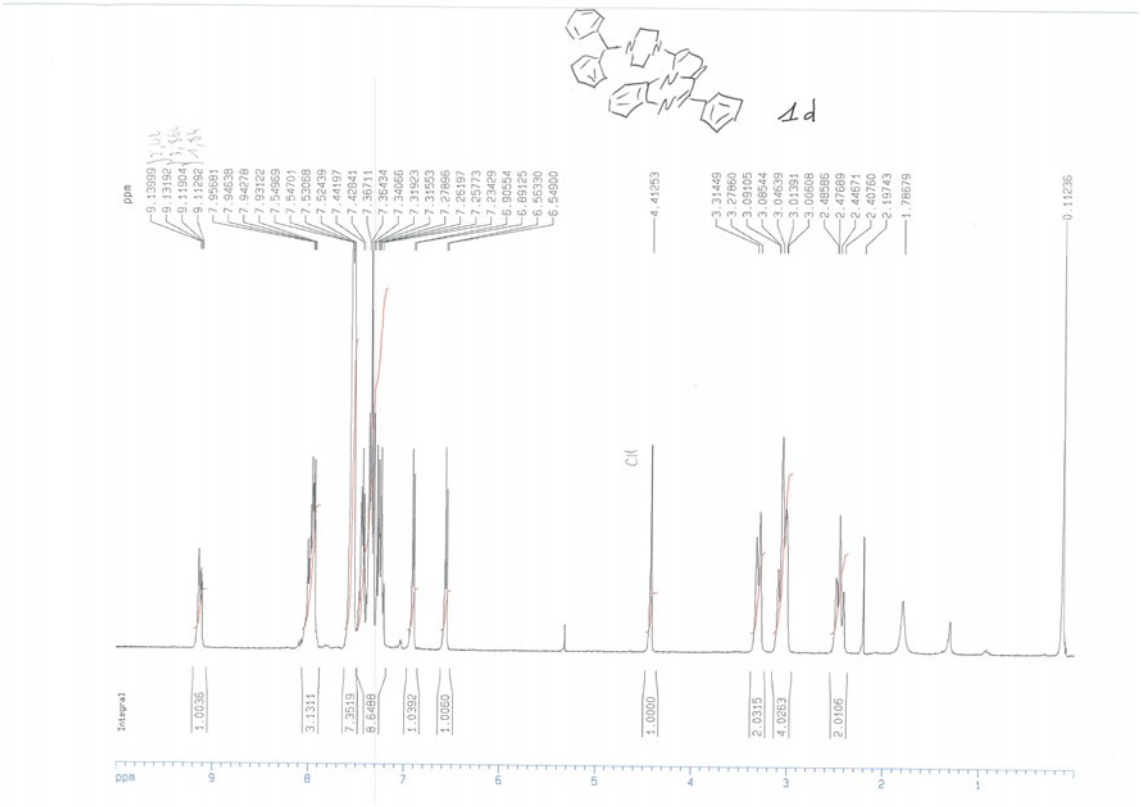

Fig. S7. ^{1}H NMR spectrum of **1d**.

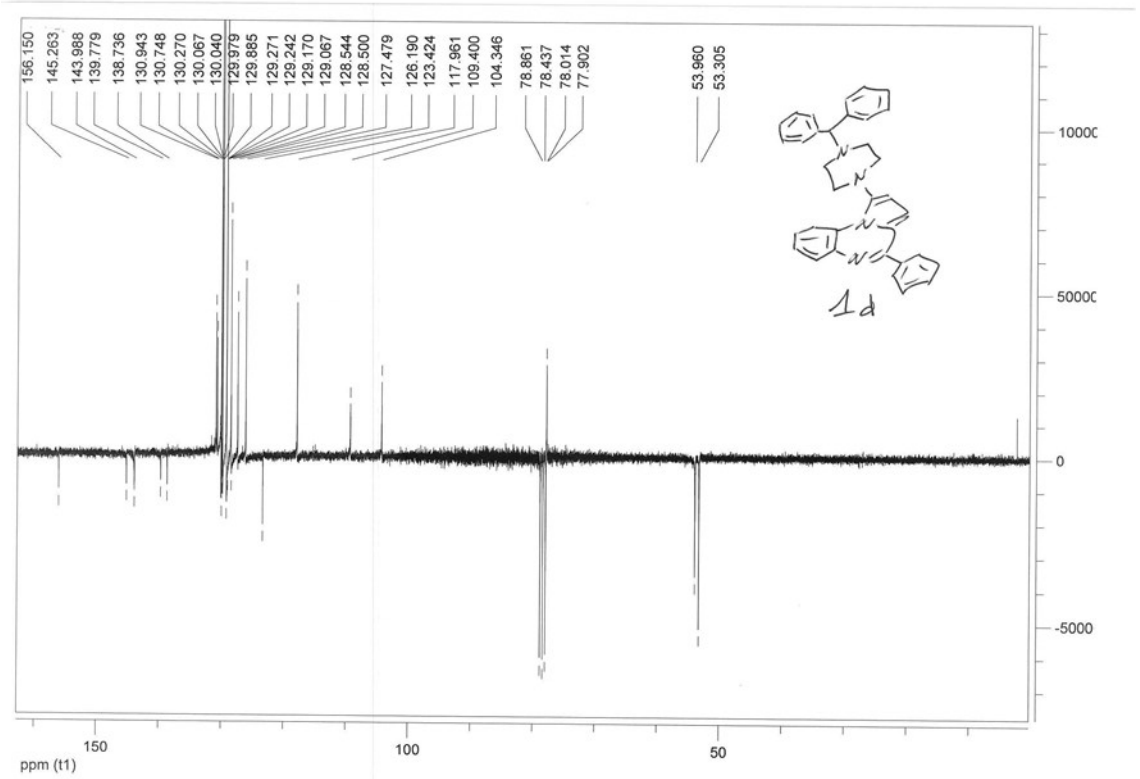

Fig. S8. ^{13}C NMR spectrum of **1d**.

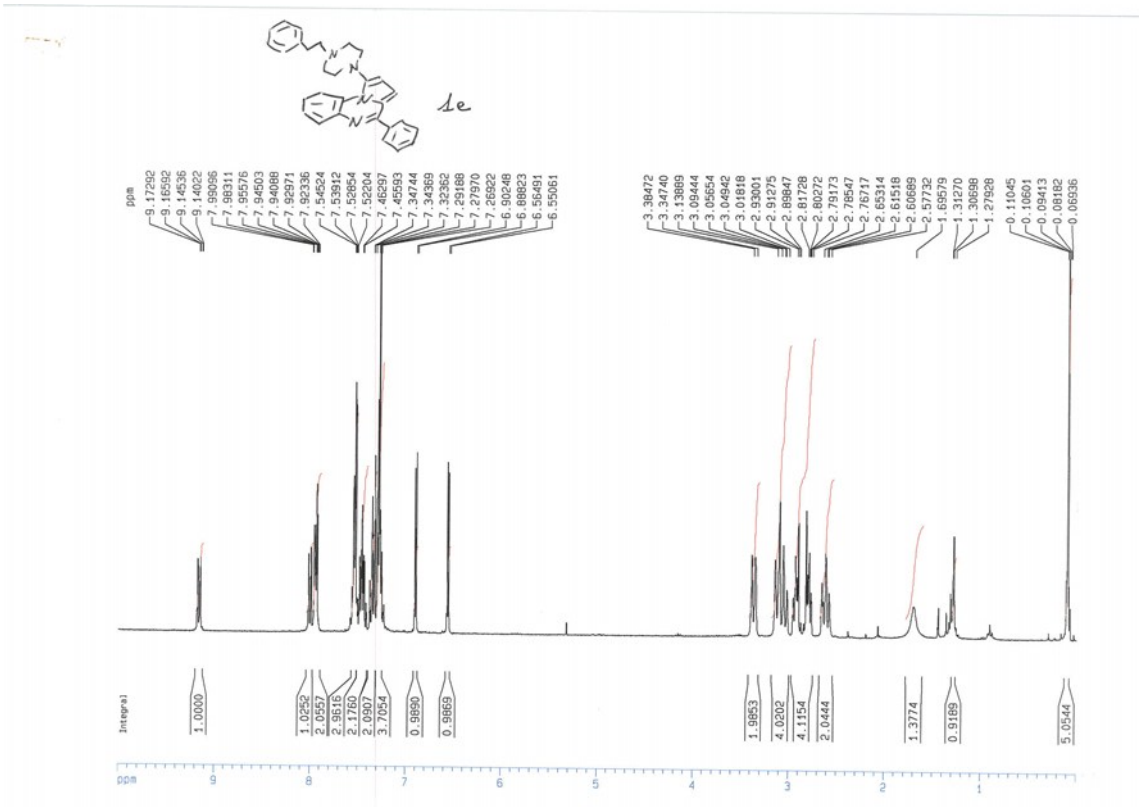

Fig. S9. ^{1}H NMR spectrum of **1e**.

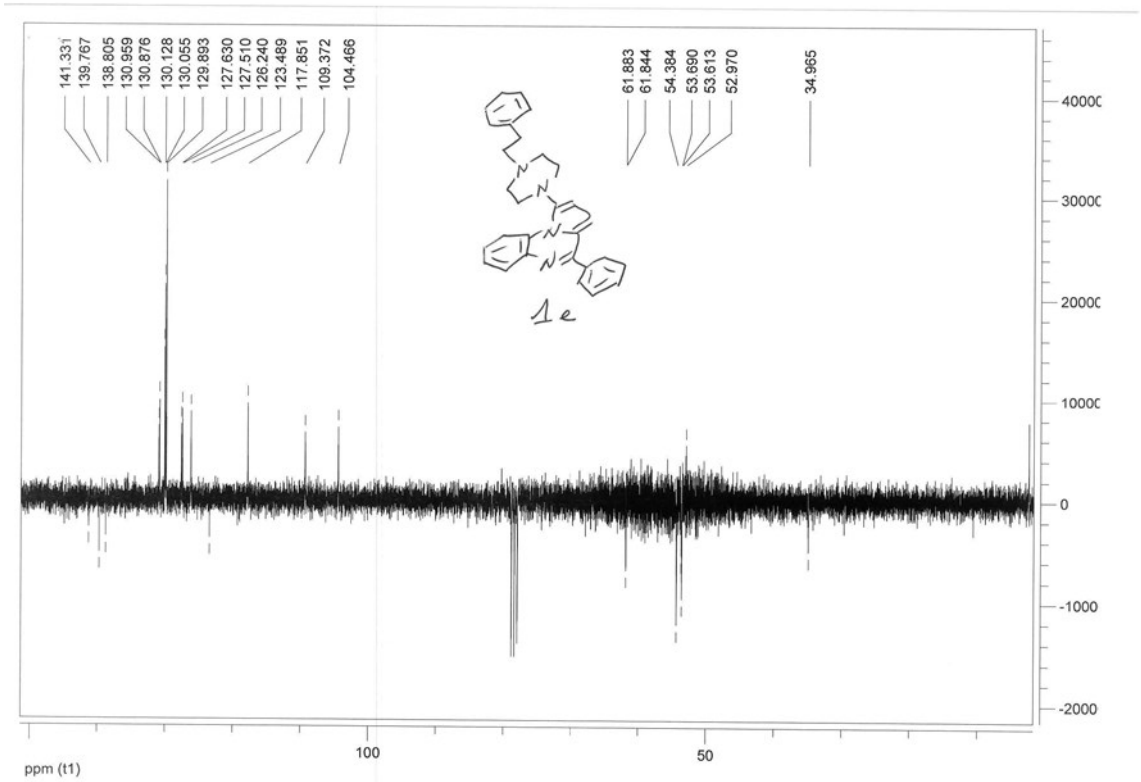

Fig. S10. ^{13}C NMR spectrum of **1e**.

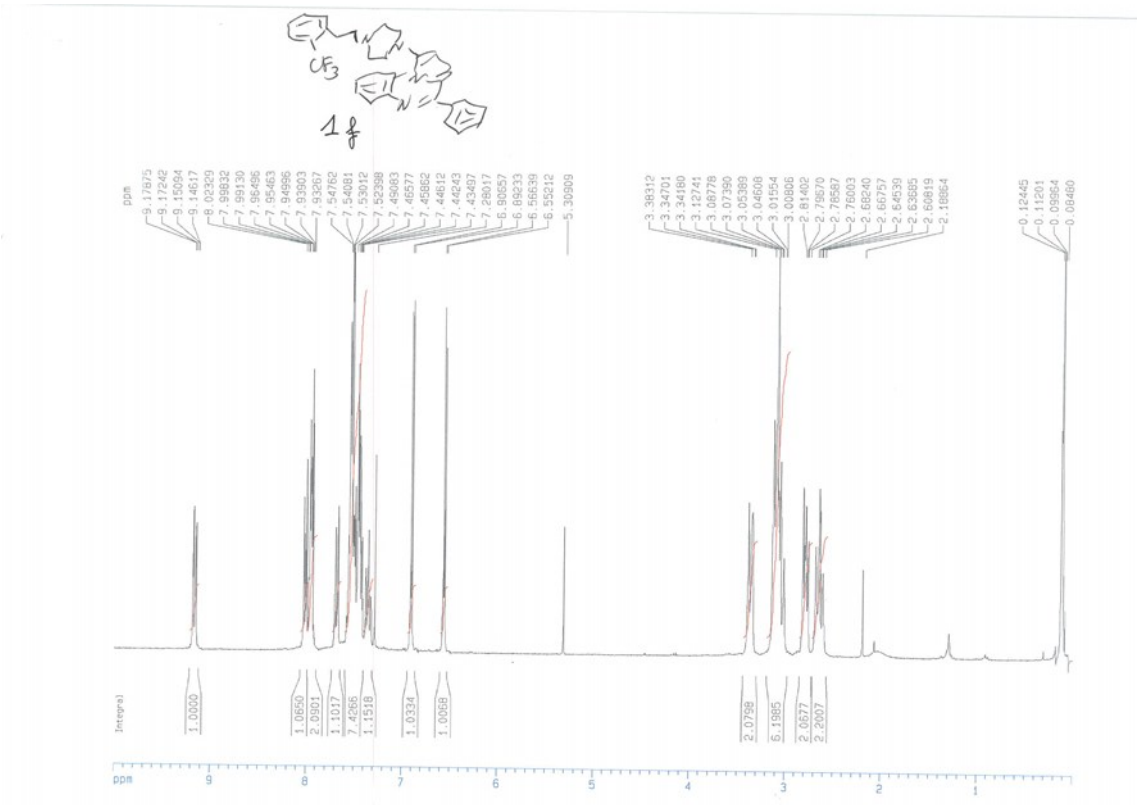

Fig. S11. ^{1}H NMR spectrum of **1f**.

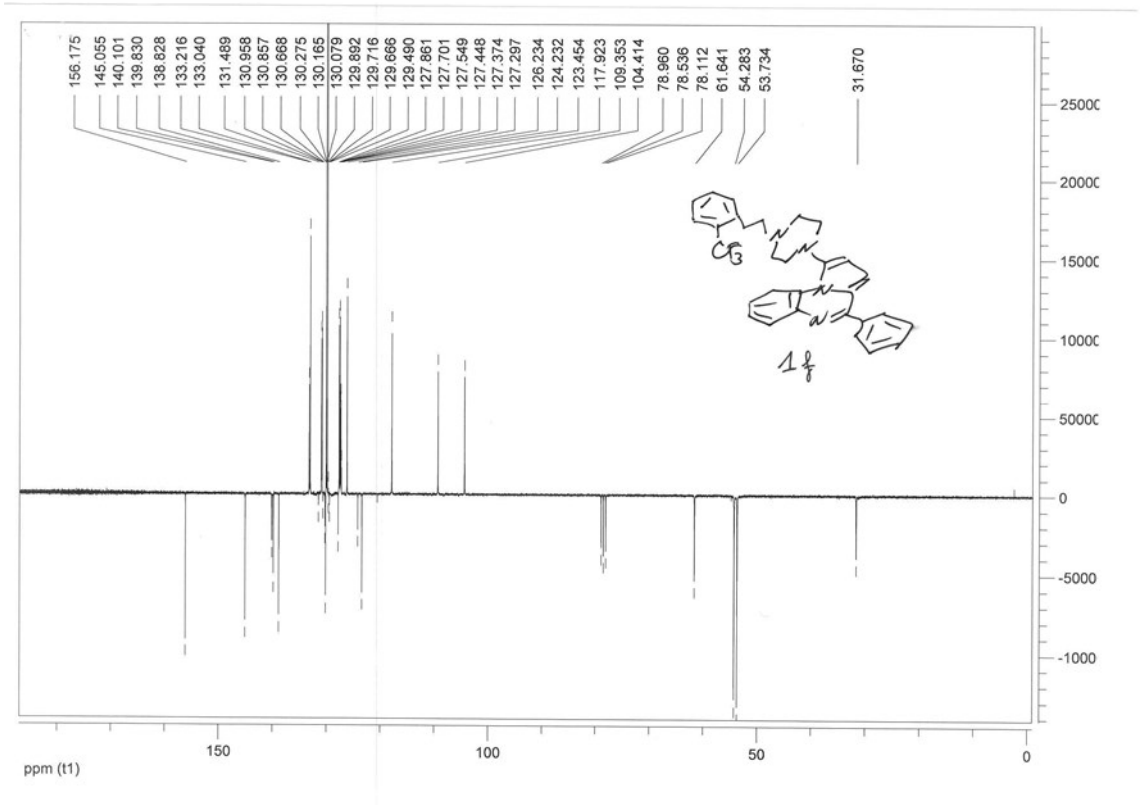

Fig. S12. ^{13}C NMR spectrum of **1f**.

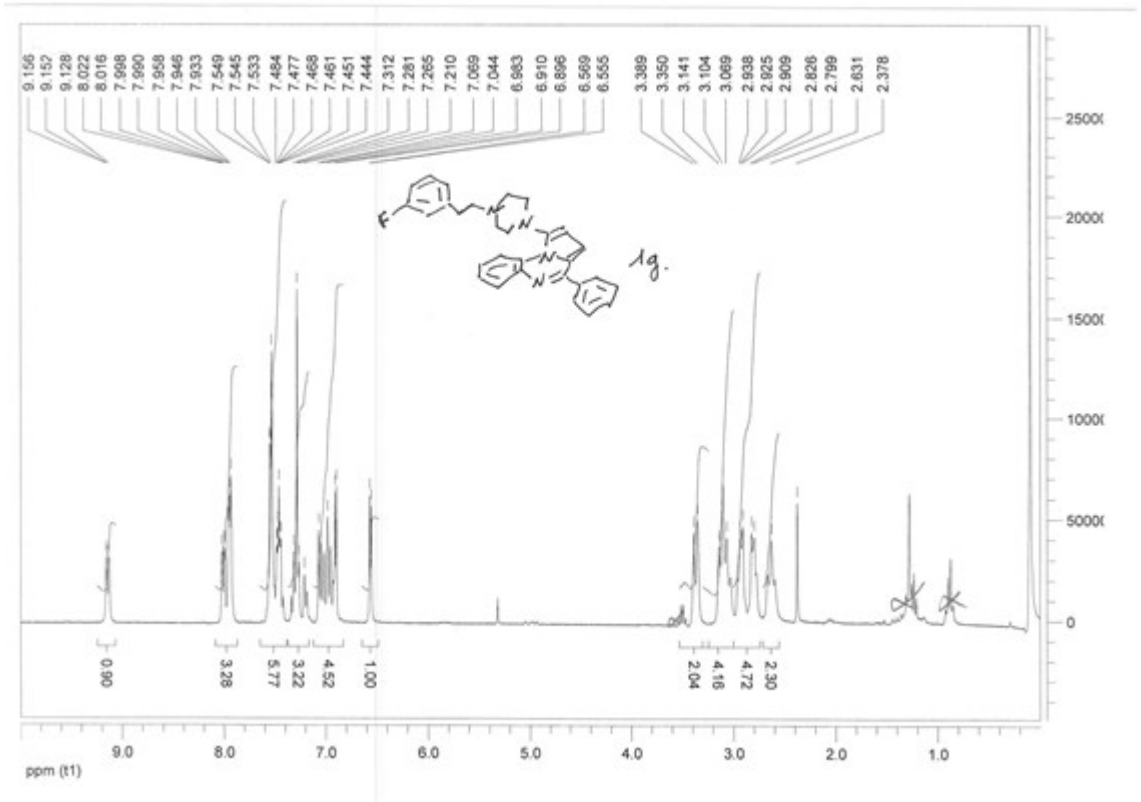

Fig. S13. ^{1}H NMR spectrum of **1g**.

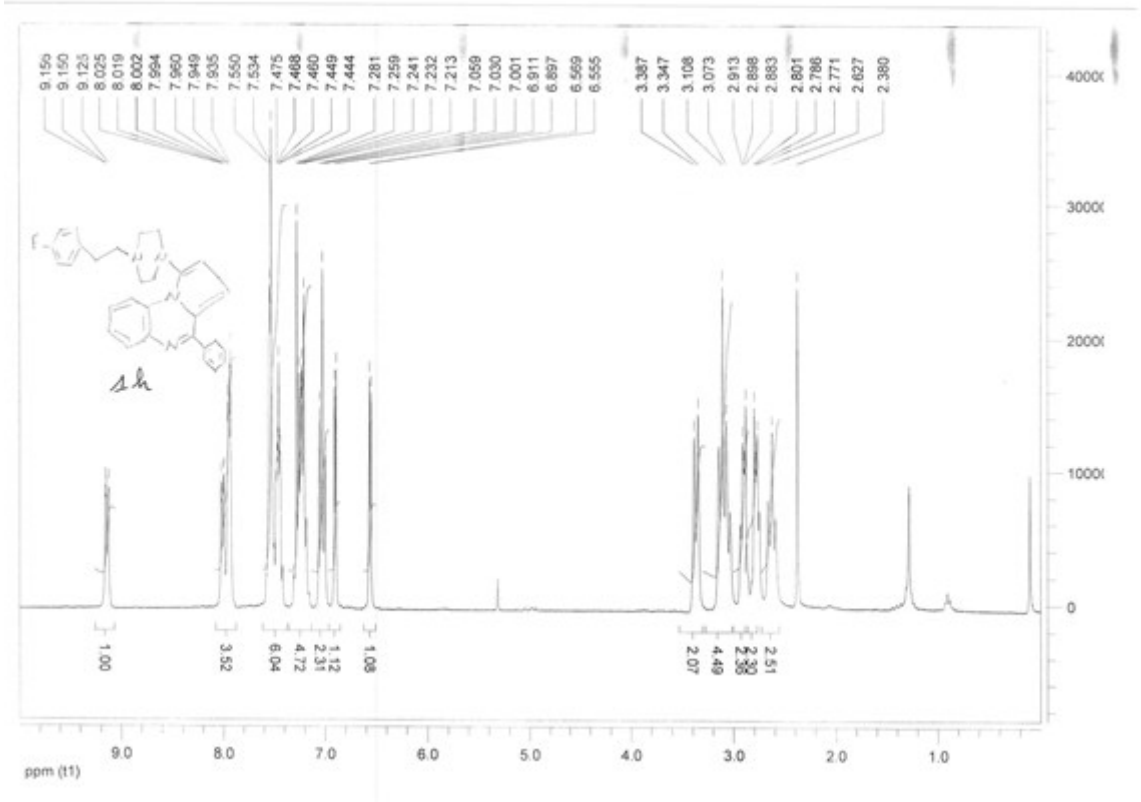

Fig. S14. [1]H NMR spectrum of **1h**.

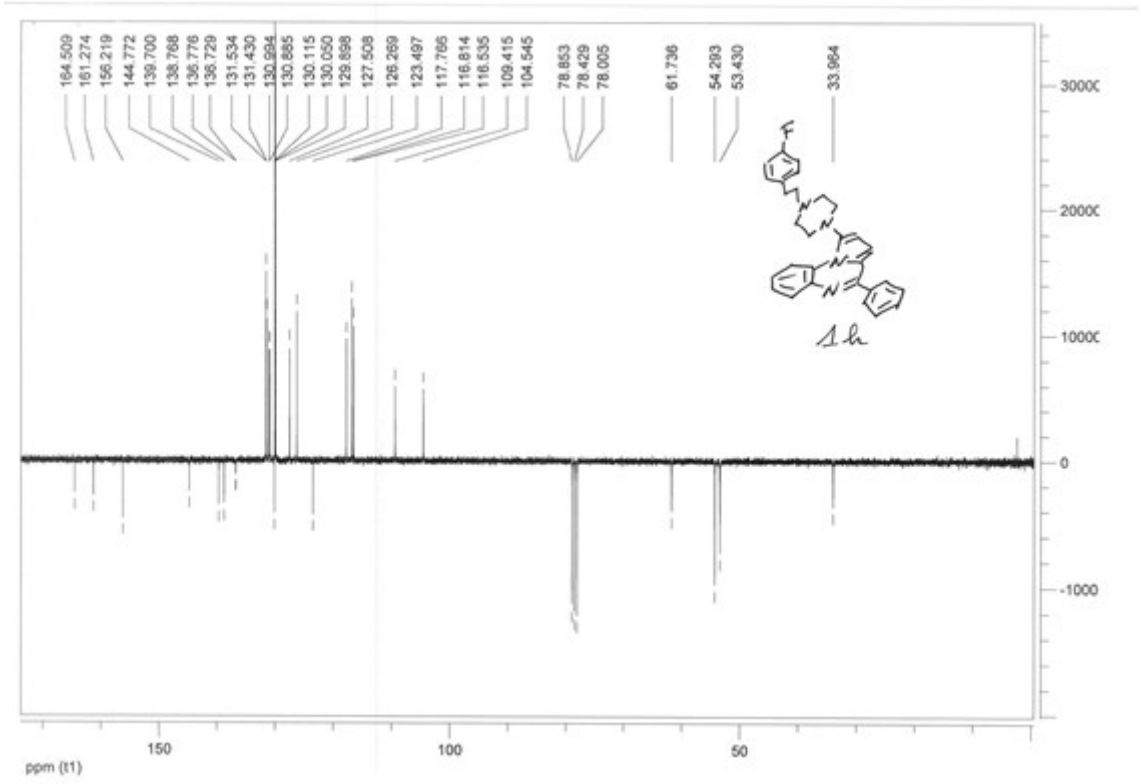

Fig. S15. ^{13}C NMR spectrum of **1h**.

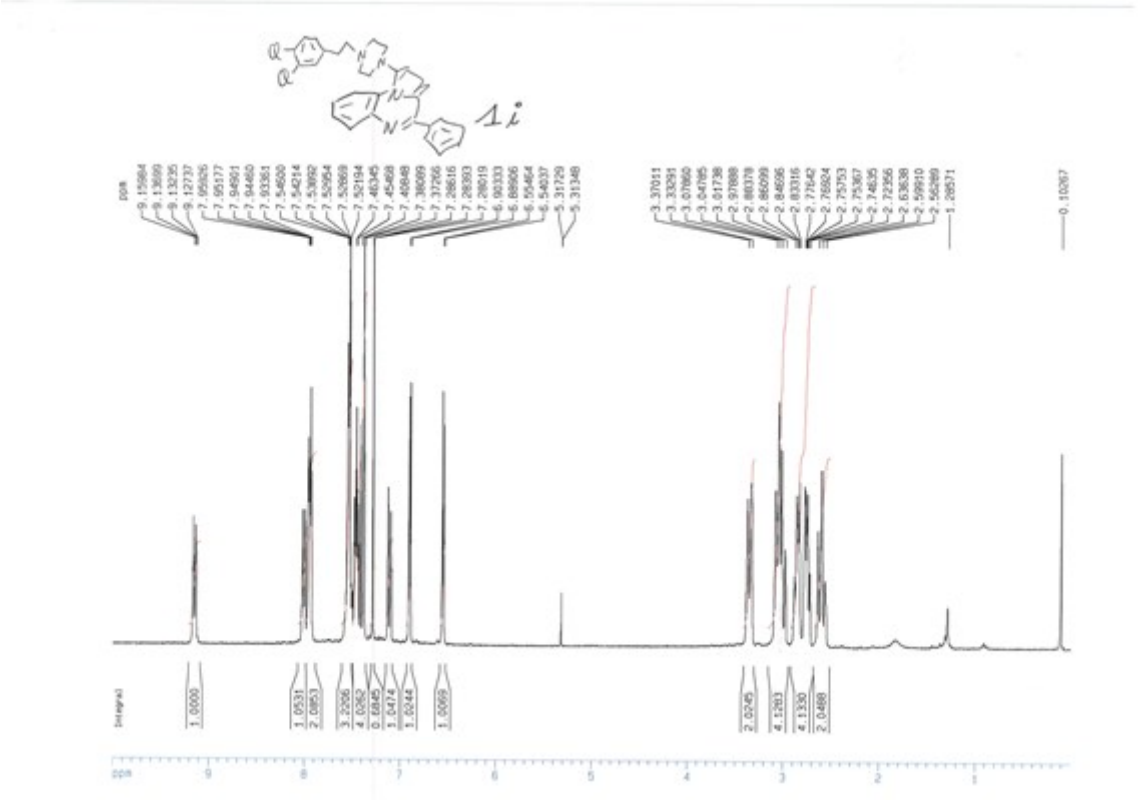

Fig. S16. ^{1}H NMR spectrum of **1i**.

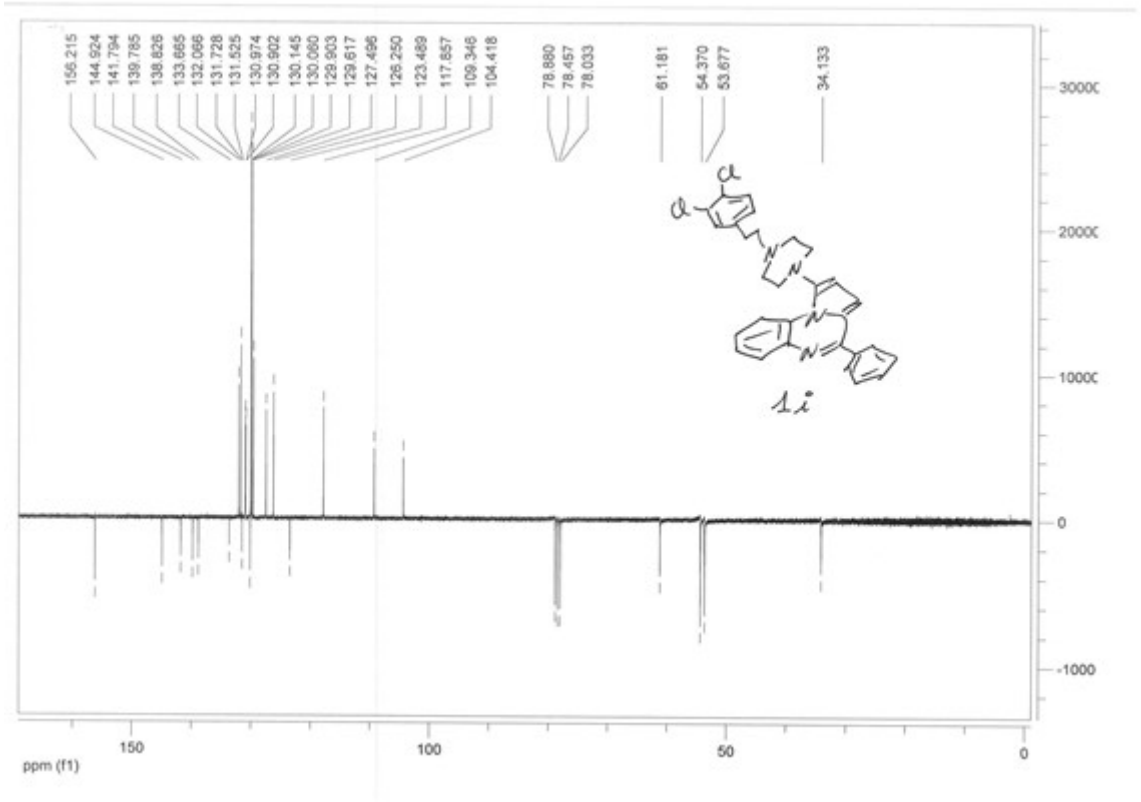

Fig. S17. ^{13}C NMR spectrum of **1i**.

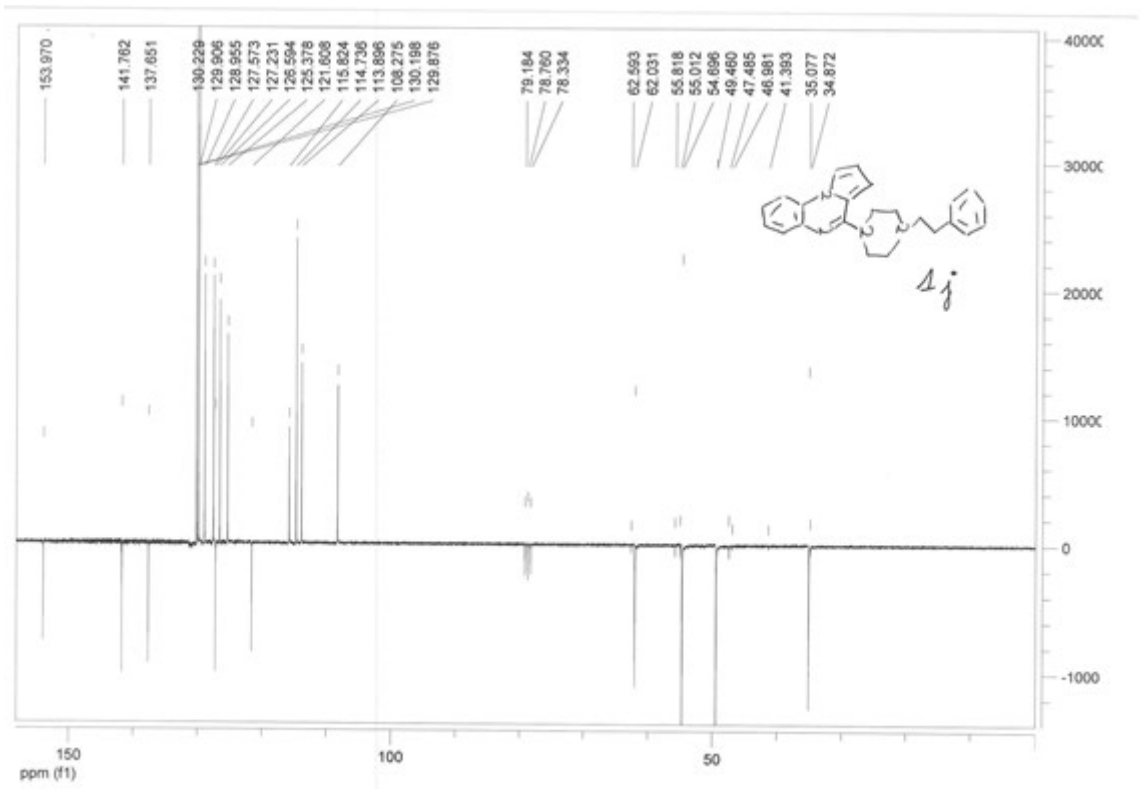

Fig. S18. ^{1}H NMR spectrum of **1j**.

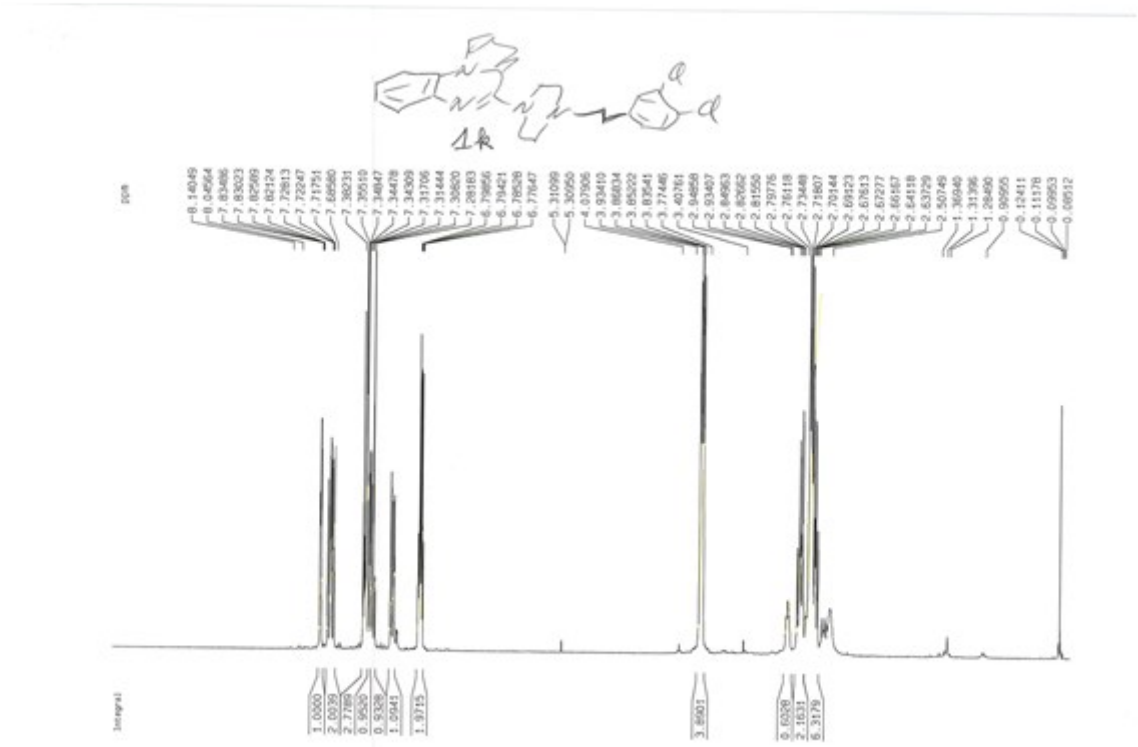

Fig. S19. ^{13}C NMR spectrum of **1j**.

Fig. S20. ^{1}H NMR spectrum of **1k**.

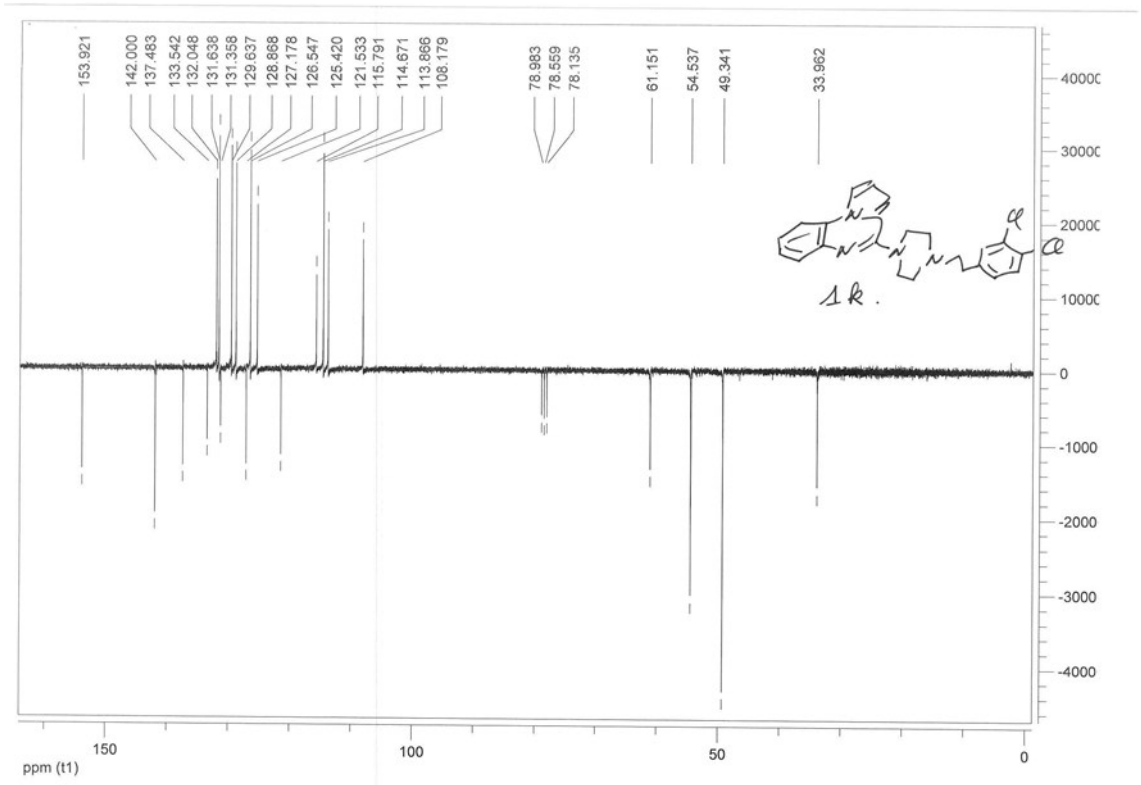

Fig. S21. ^{13}C NMR spectrum of **1k**.

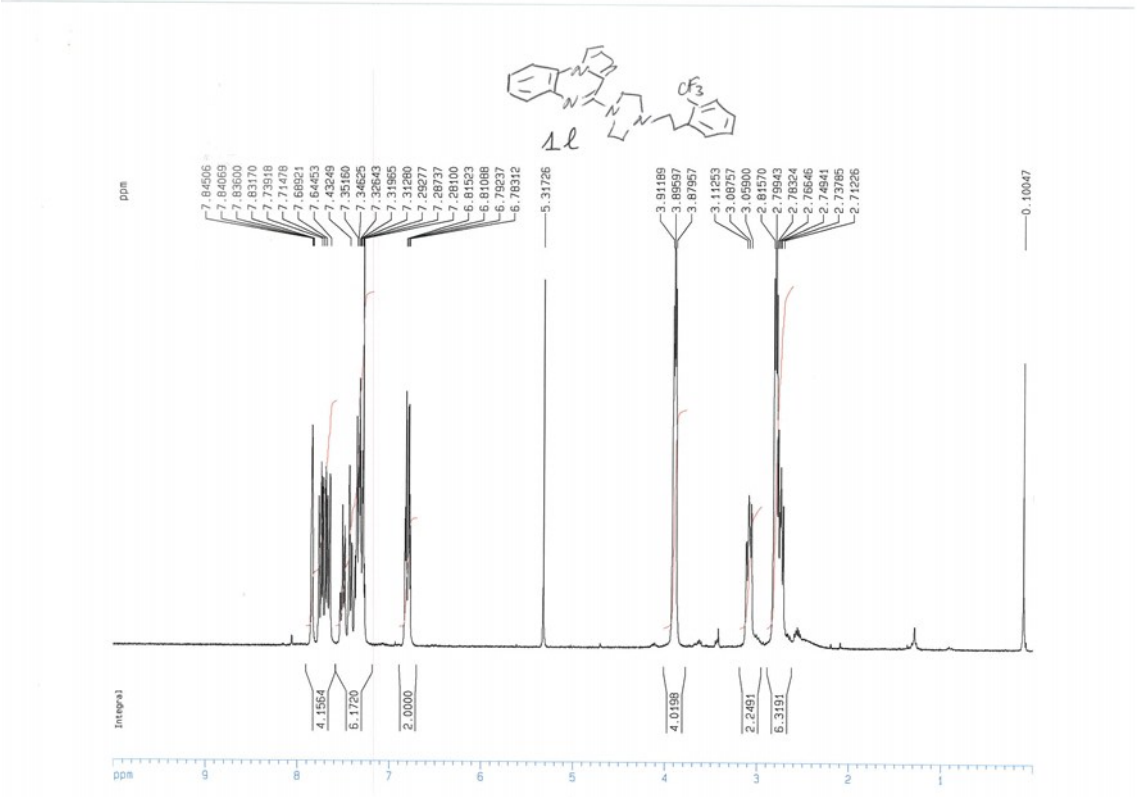

Fig. S22. ^{1}H NMR spectrum of **1l**.

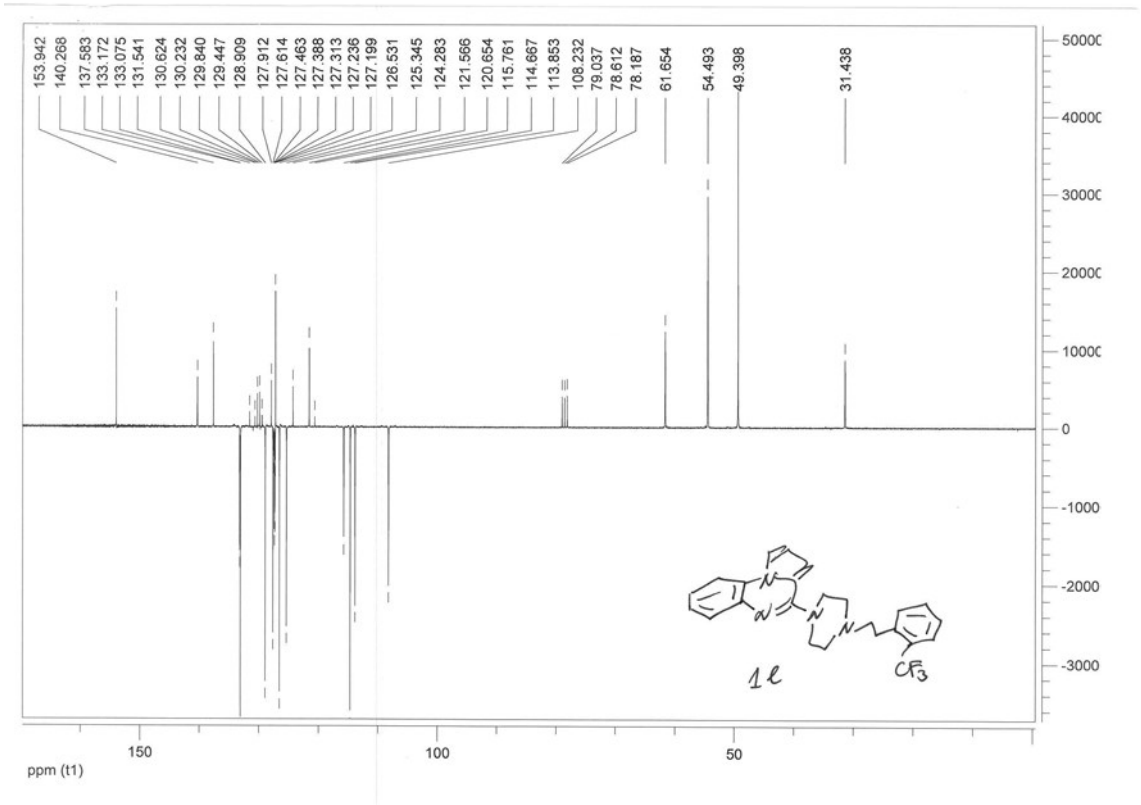

Fig. S23. ^{13}C NMR spectrum of **1l**.

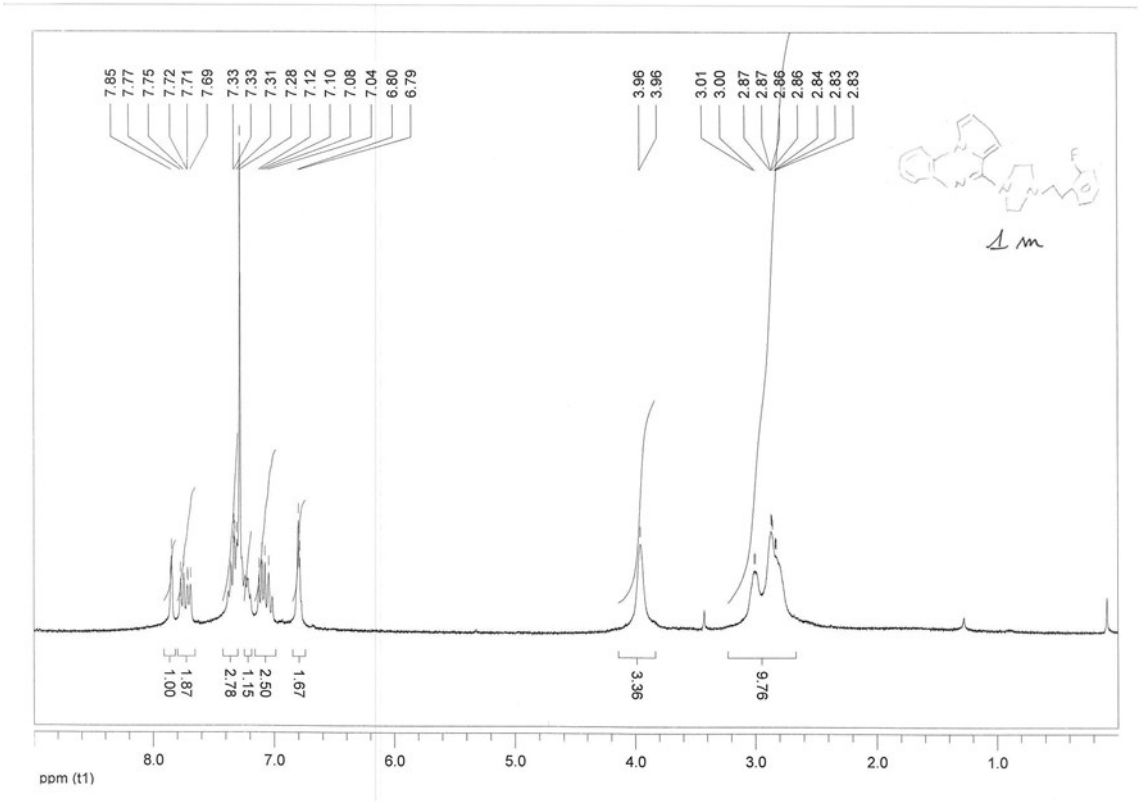

Fig. S24. ^{1}H NMR spectrum of **1m**.

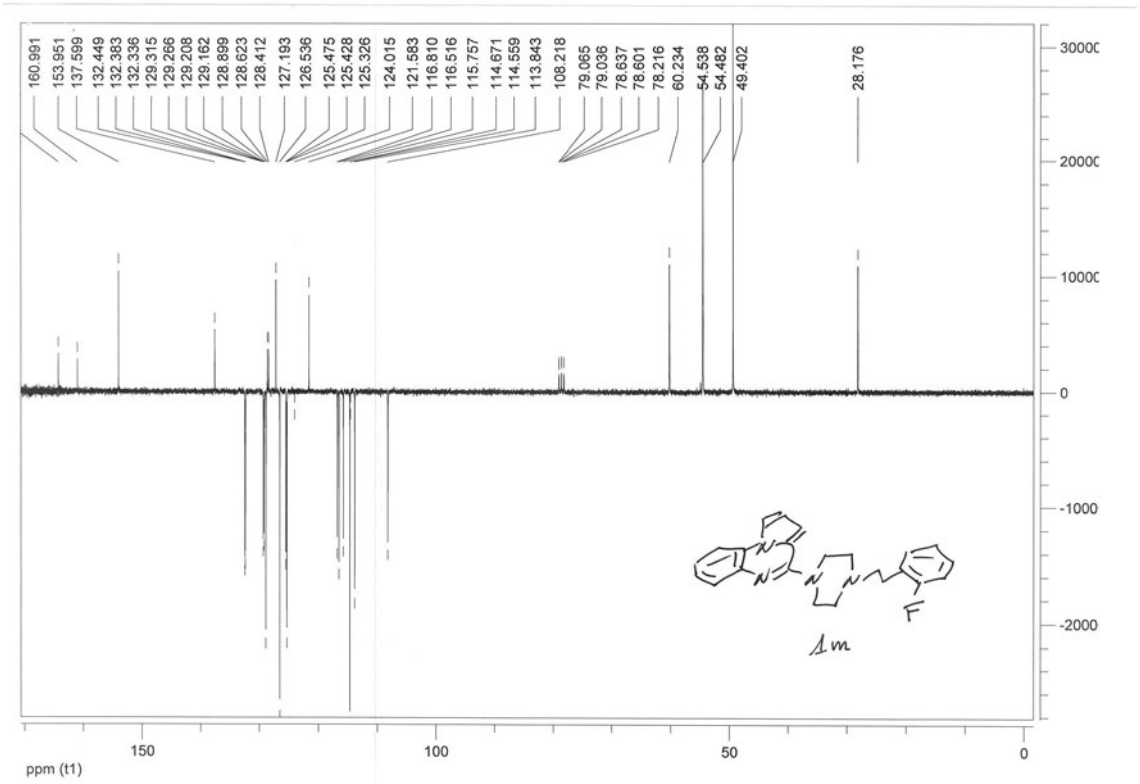

Fig. S25. ^{13}C NMR spectrum of **1m**.

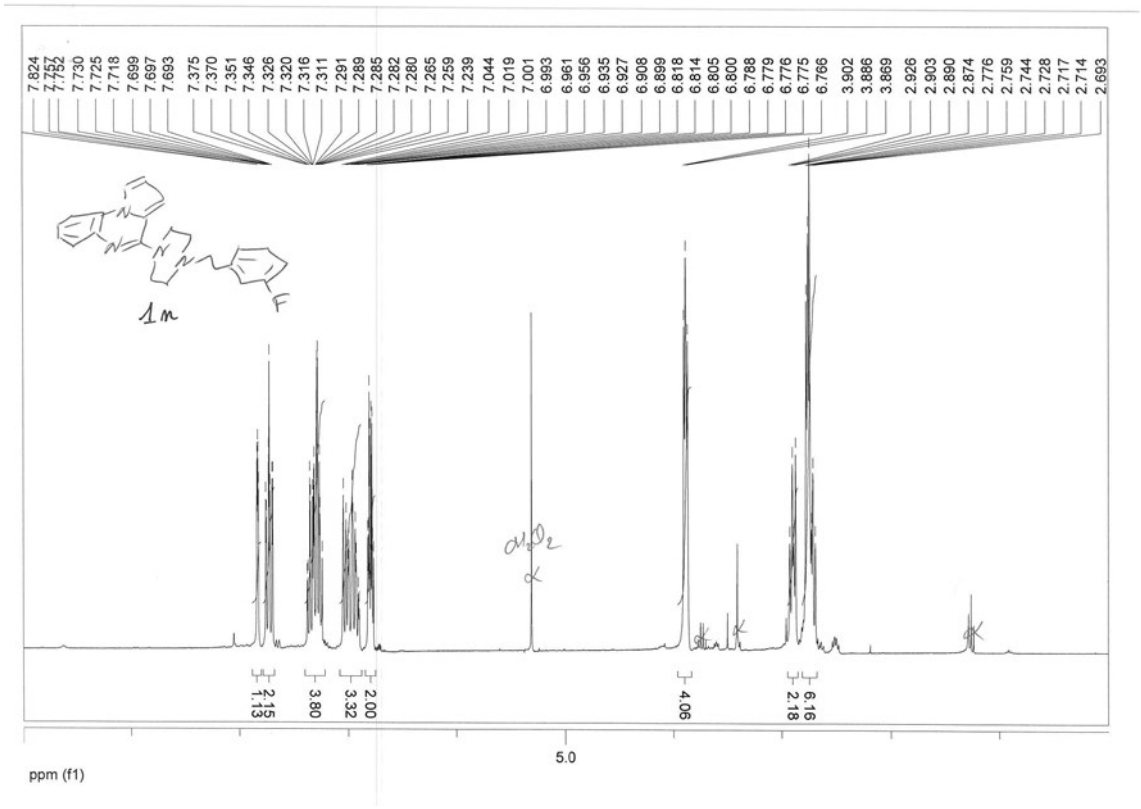

Fig. S26. ^{1}H NMR spectrum of **1n**.

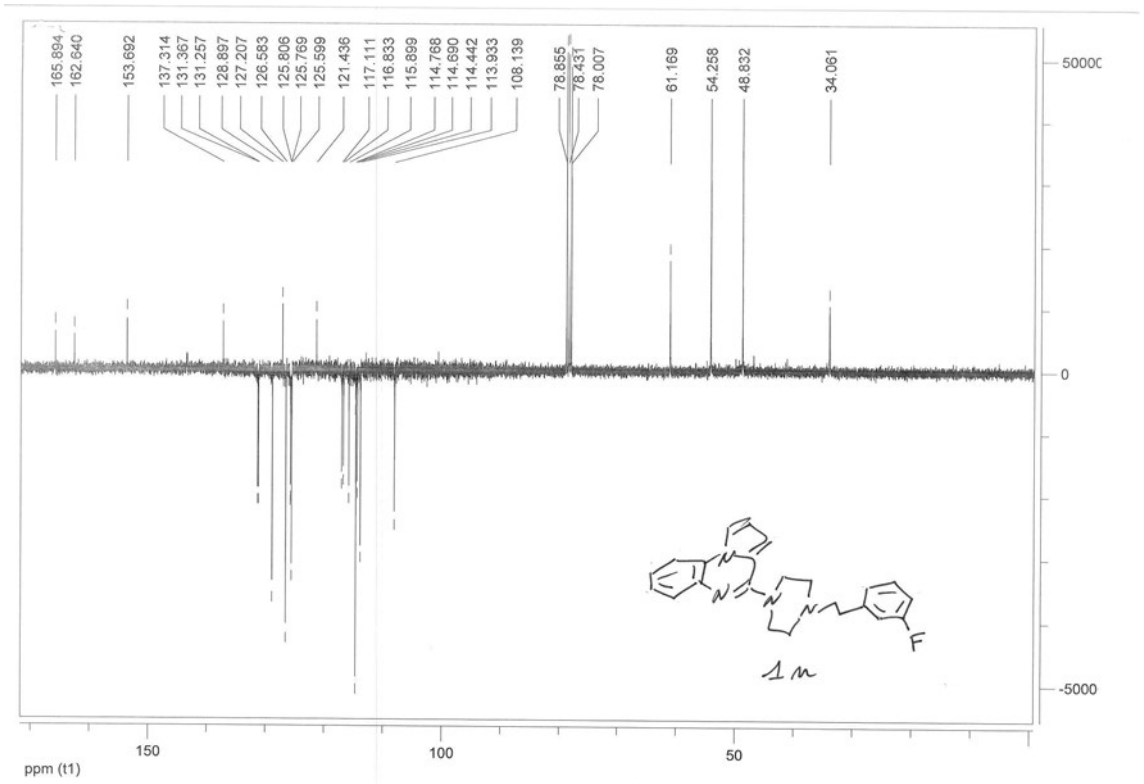

Fig. S27. ^{13}C NMR spectrum of **1n**.

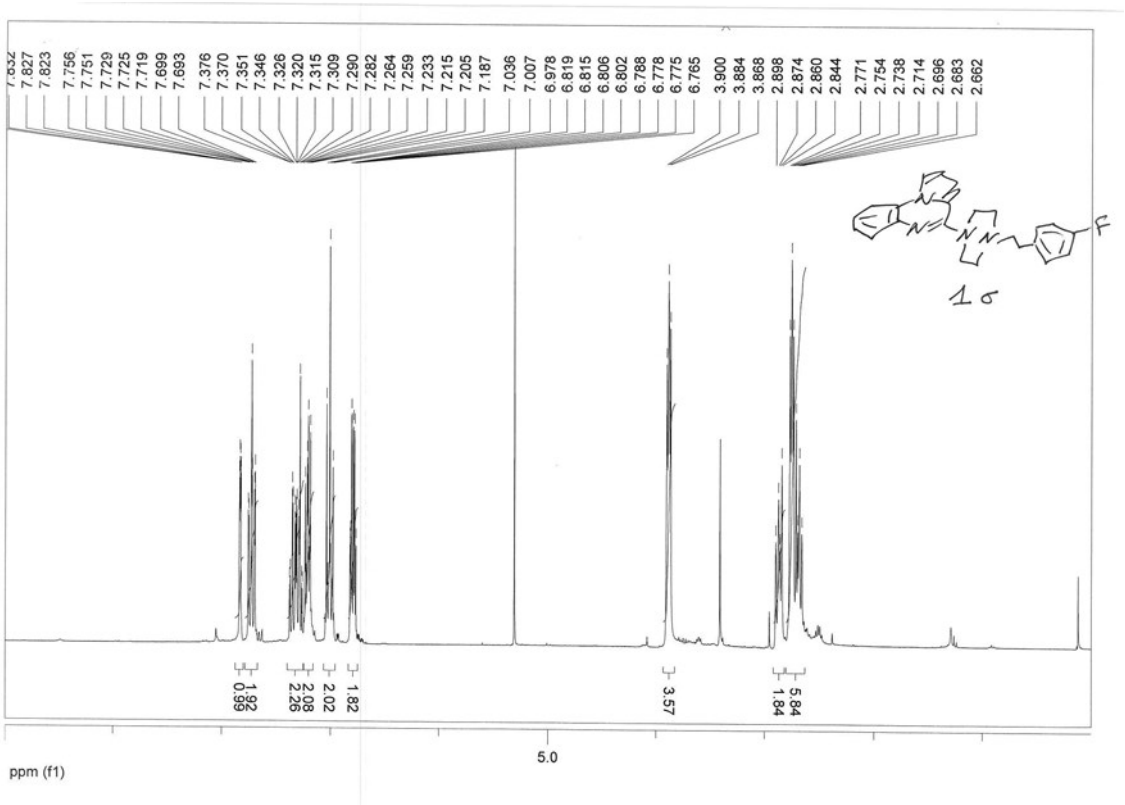

Fig. S28. [1]H NMR spectrum of **1o**.

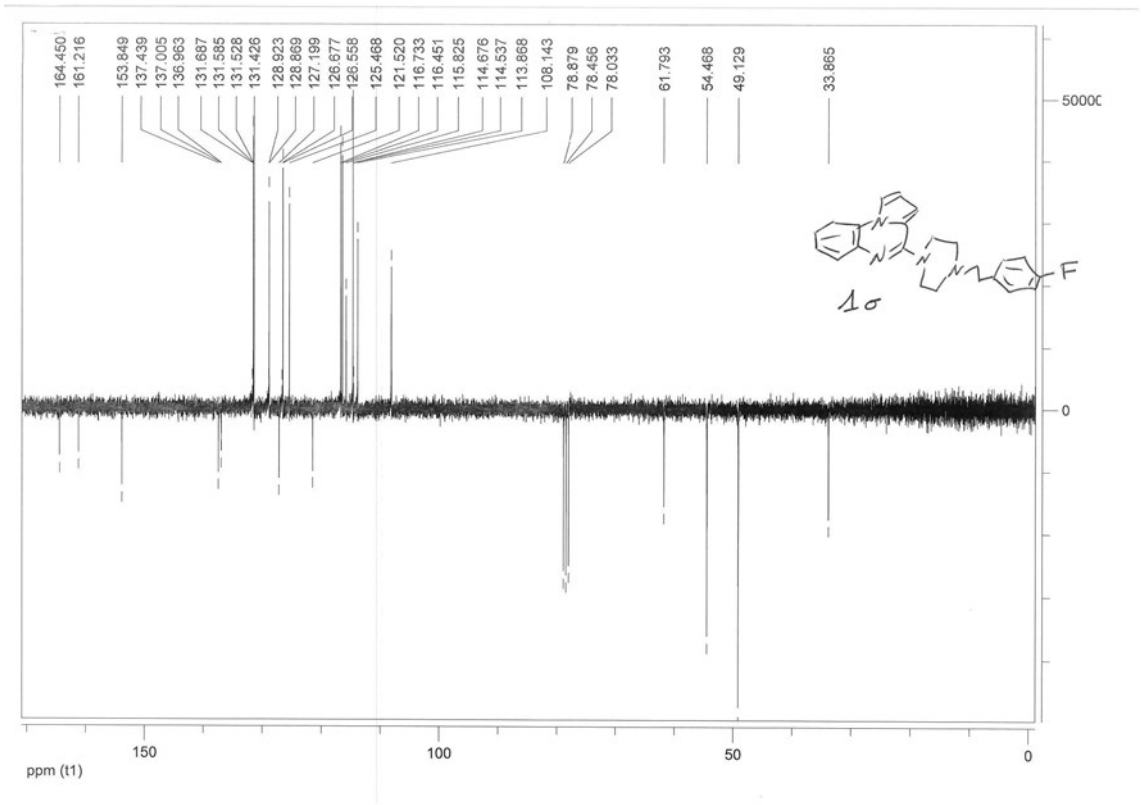

Fig. S29. ^{13}C NMR spectrum of **1o**.

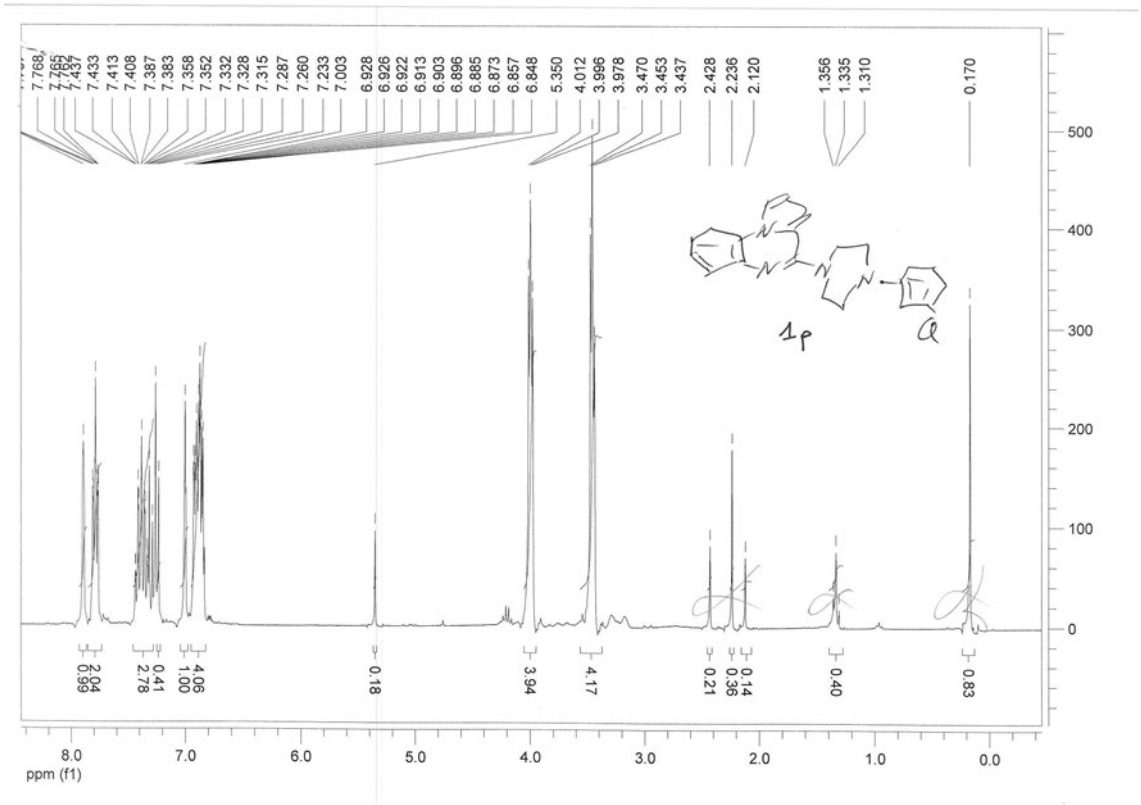

Fig. S30. ^{1}H NMR spectrum of **1p**.

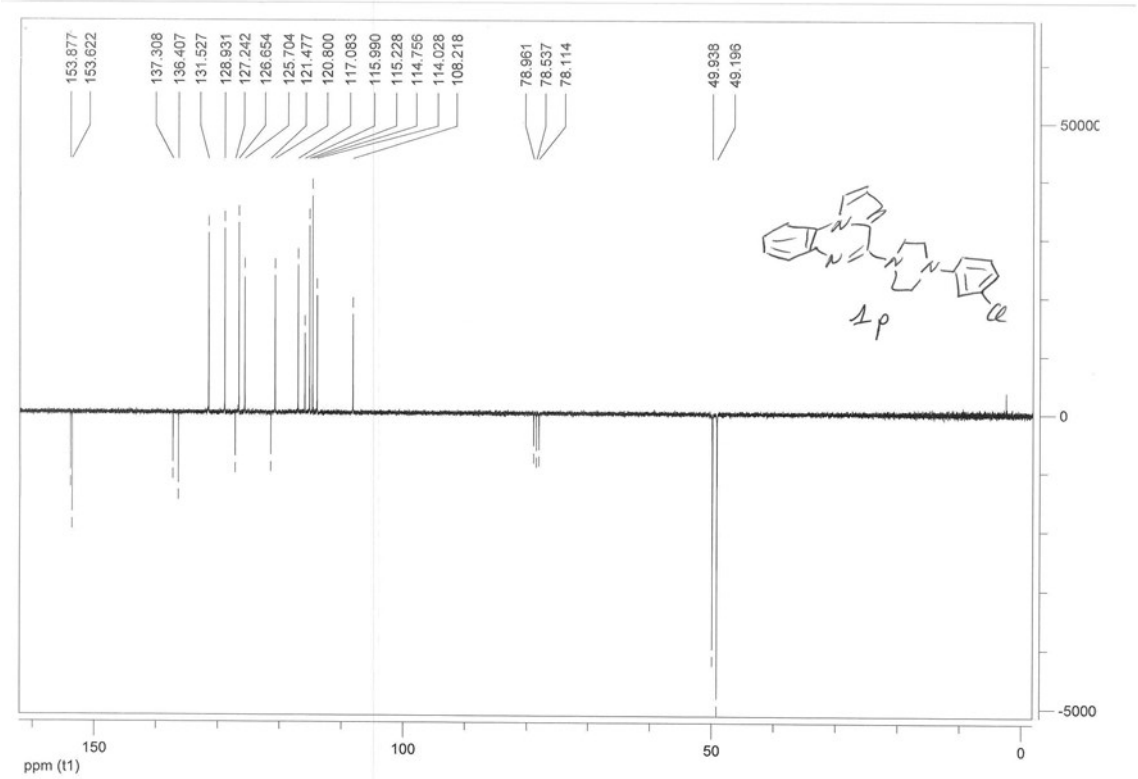

Fig. S31. ^{13}C NMR spectrum of **1p**.

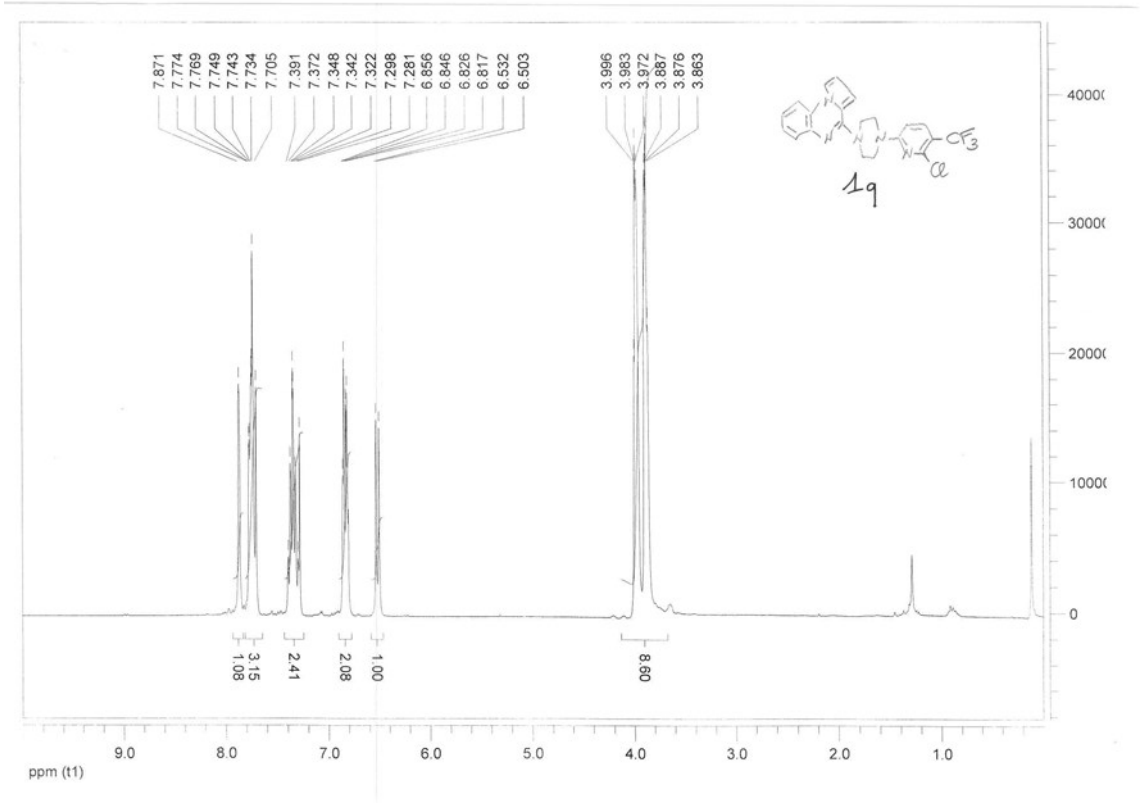

Fig. S32. ^{1}H NMR spectrum of **1q**.

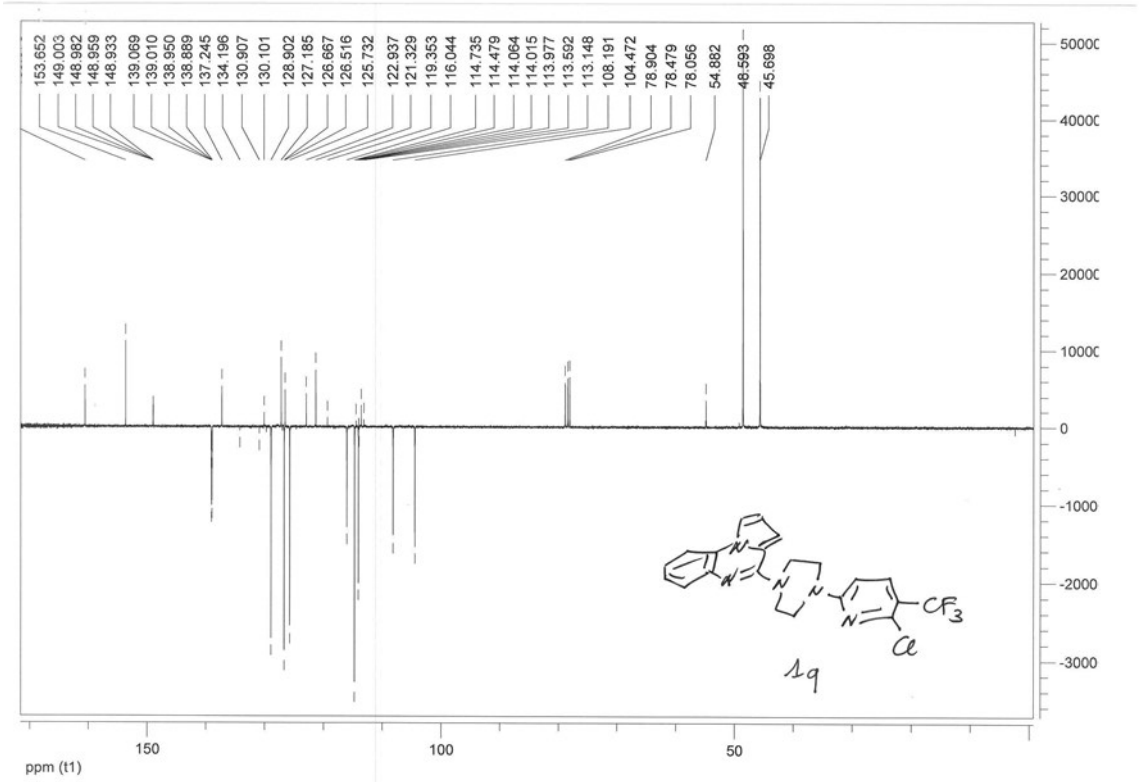

Fig. S33. ^{13}C NMR spectrum of **1q**.

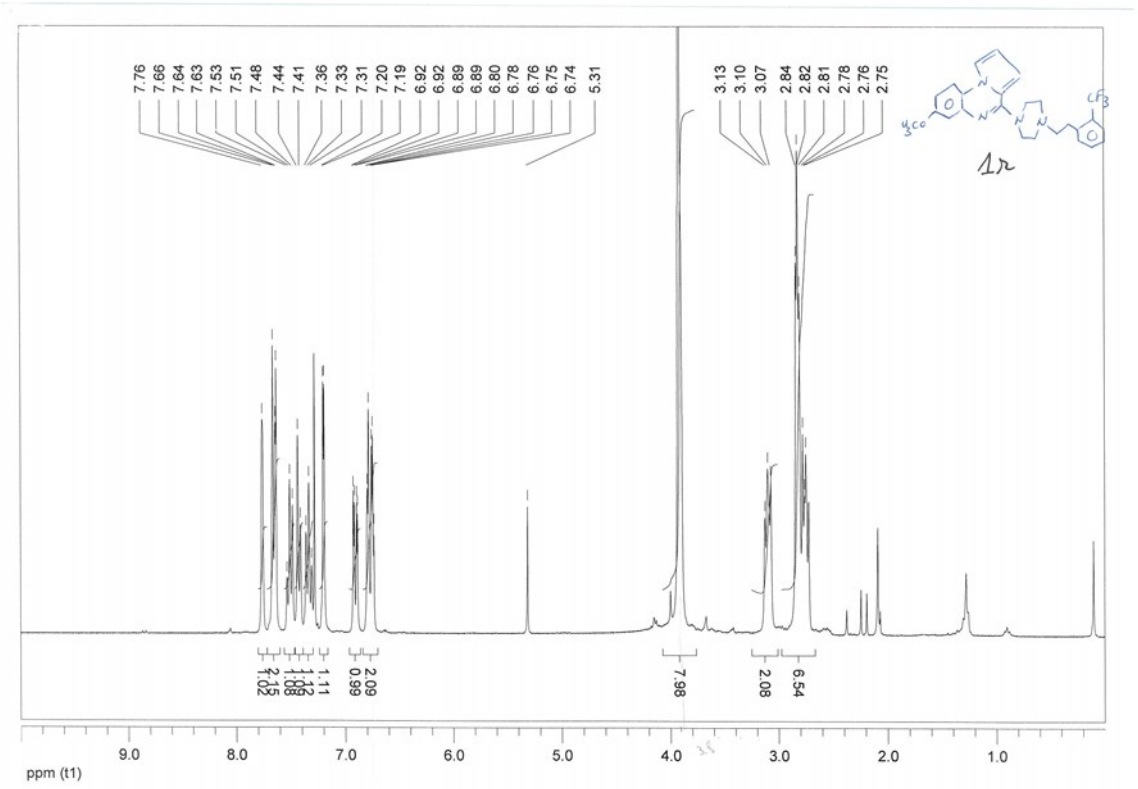

Fig. S34. ^{1}H NMR spectrum of **1r**.

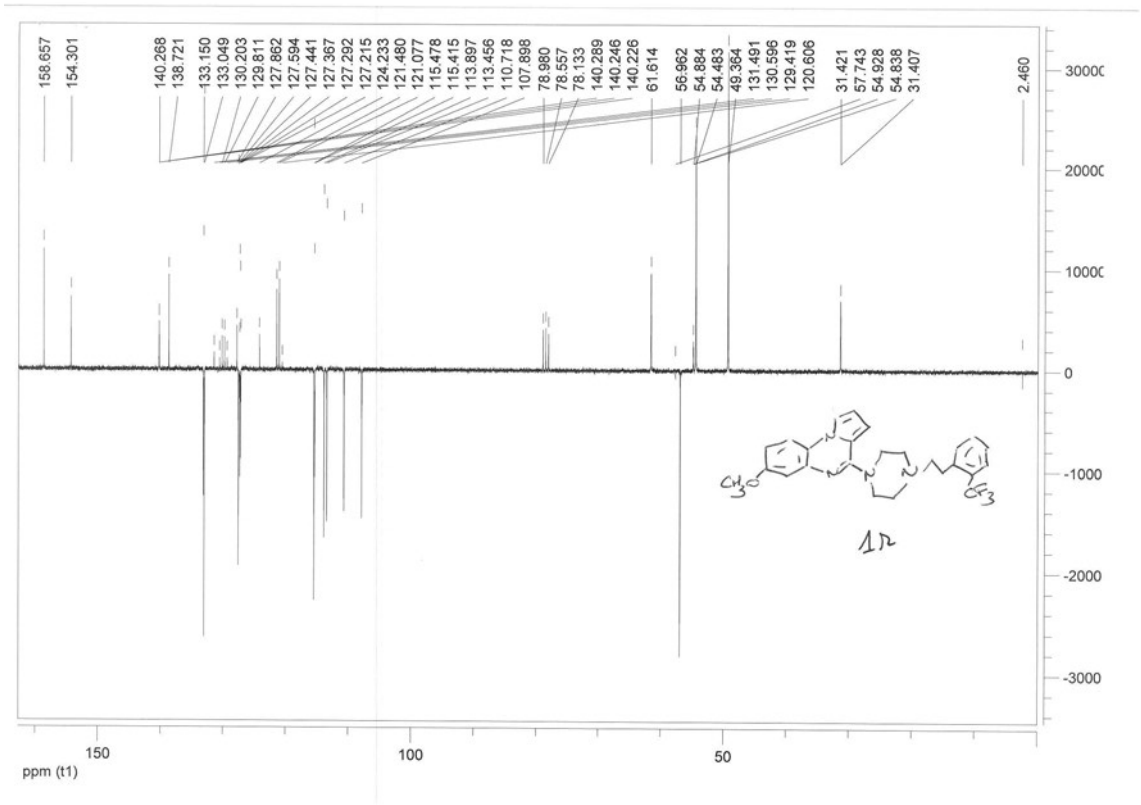

Fig. S35. ^{13}C NMR spectrum of **1r**.

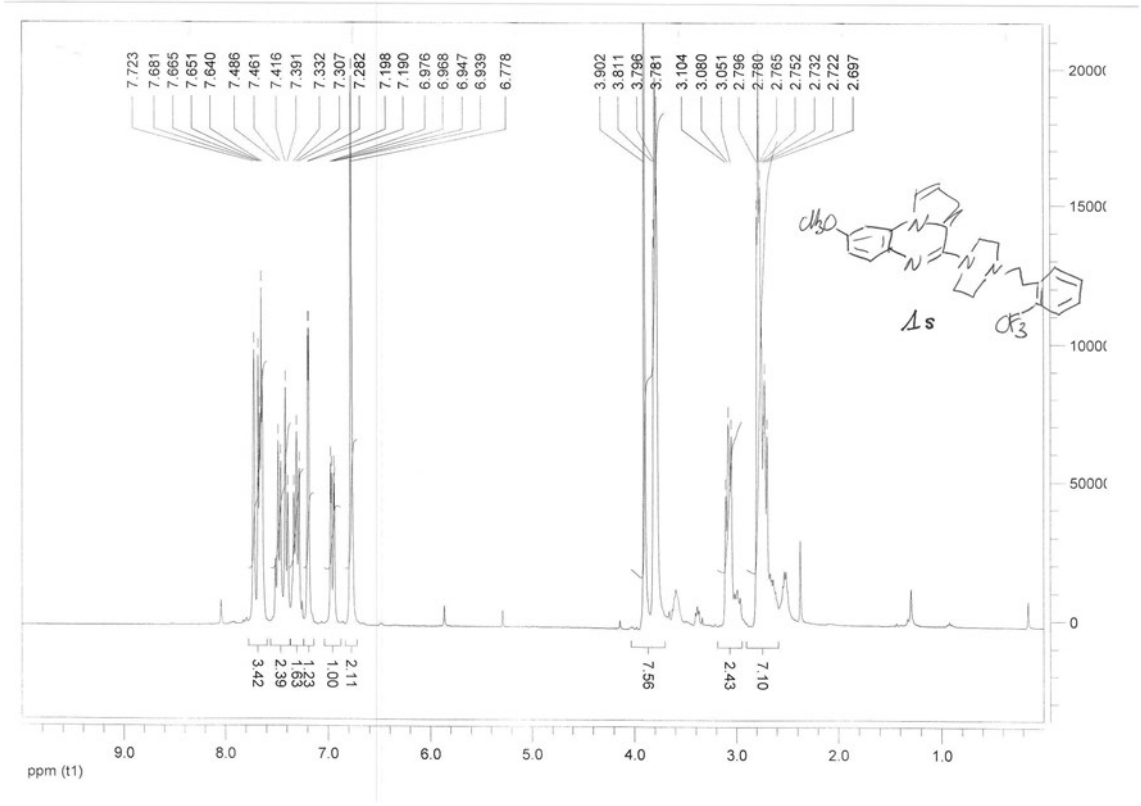

Fig. S36. ^{1}H NMR spectrum of **1s**.

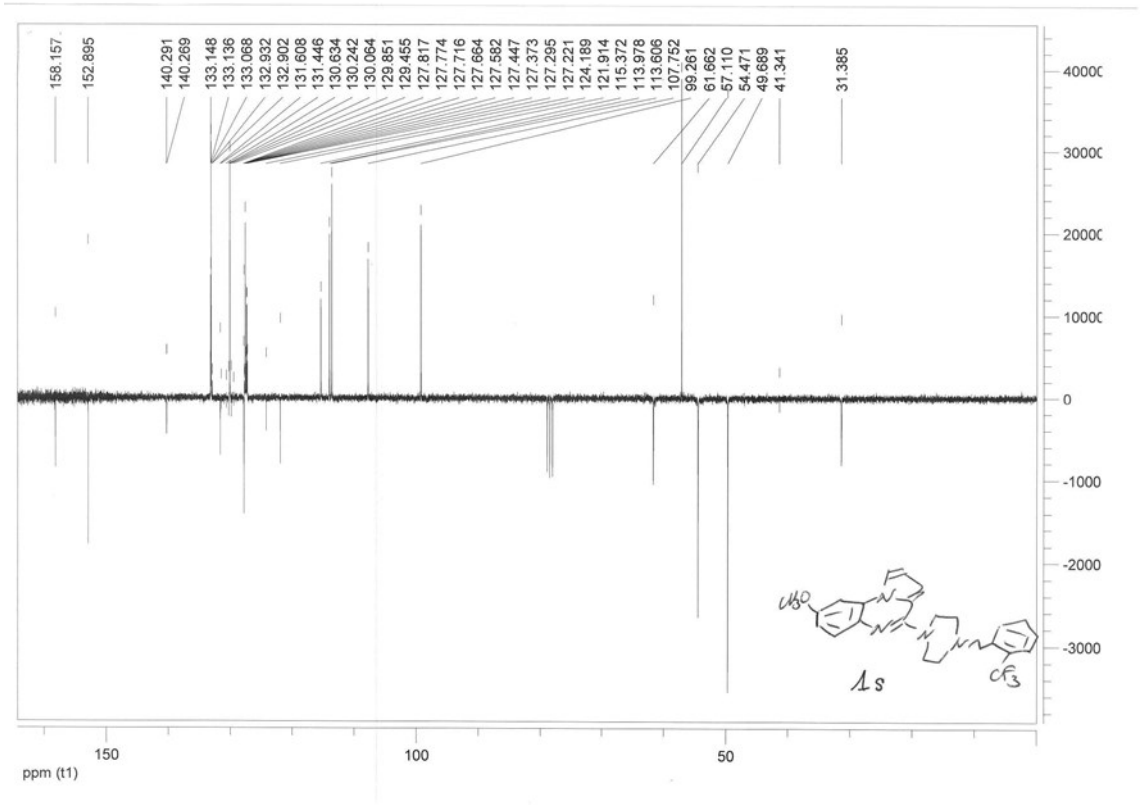

Fig. S37. ^{13}C NMR spectrum of **1s**.

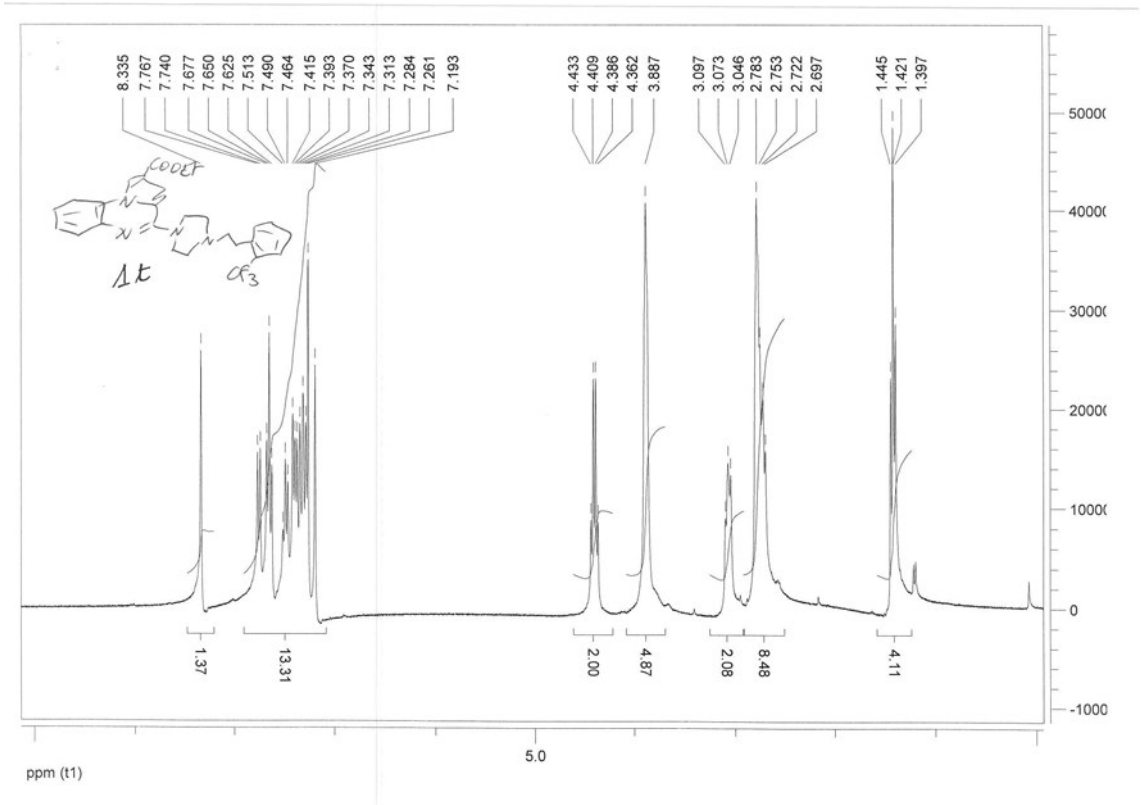

Fig.S38. [1]H NMR spectrum of **1t**.

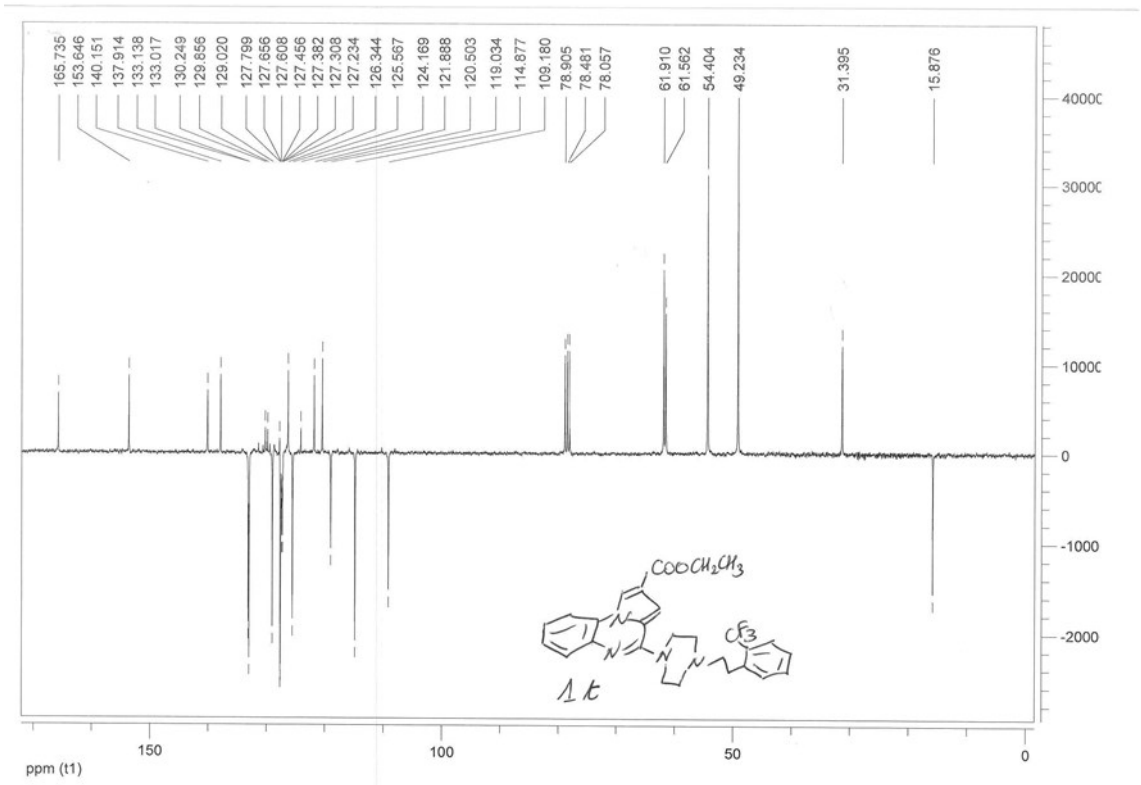

Fig.S39. ^{13}C NMR spectrum of **1t**.

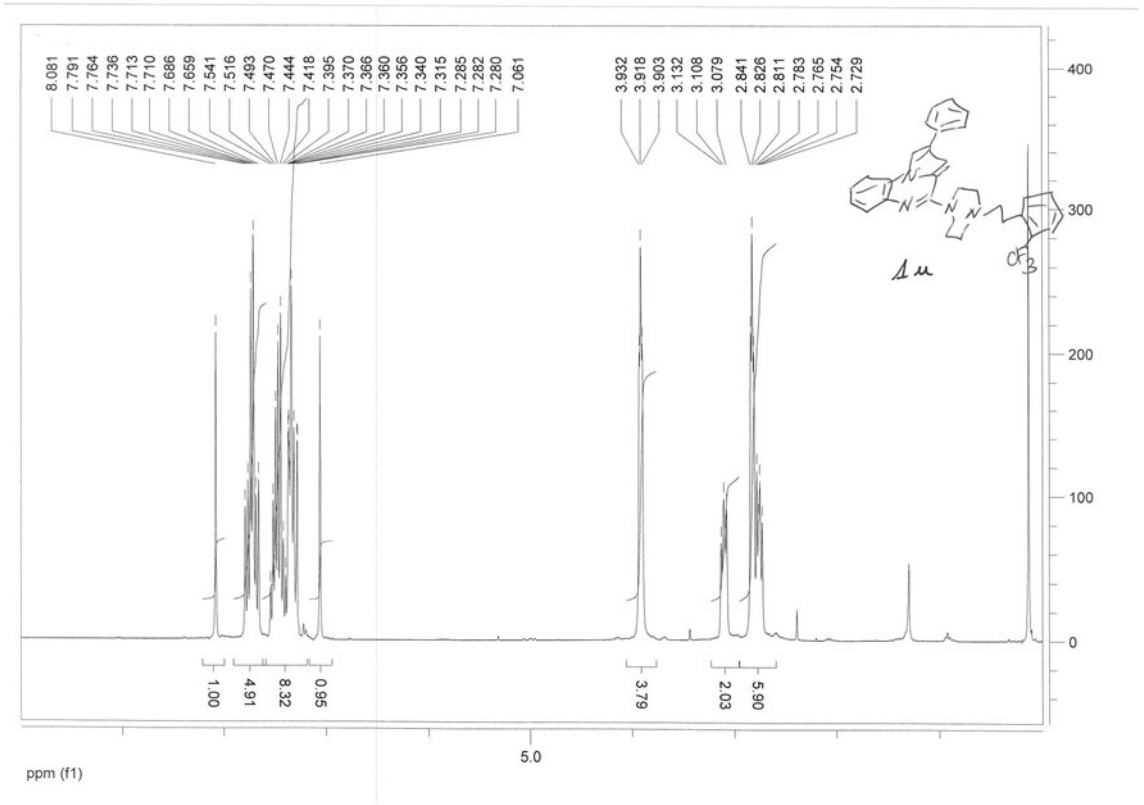

Fig. S40. ^{1}H NMR spectrum of **1u**.

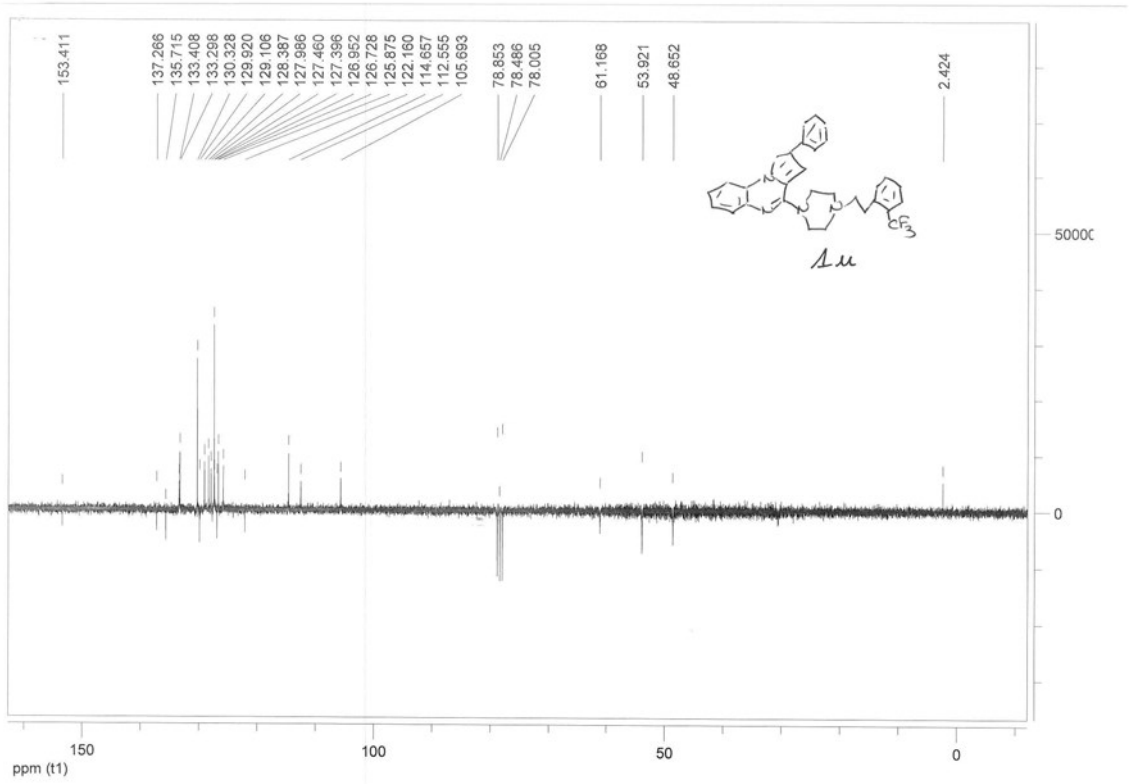

Fig. S41. ^{13}C NMR spectrum of **1u**.

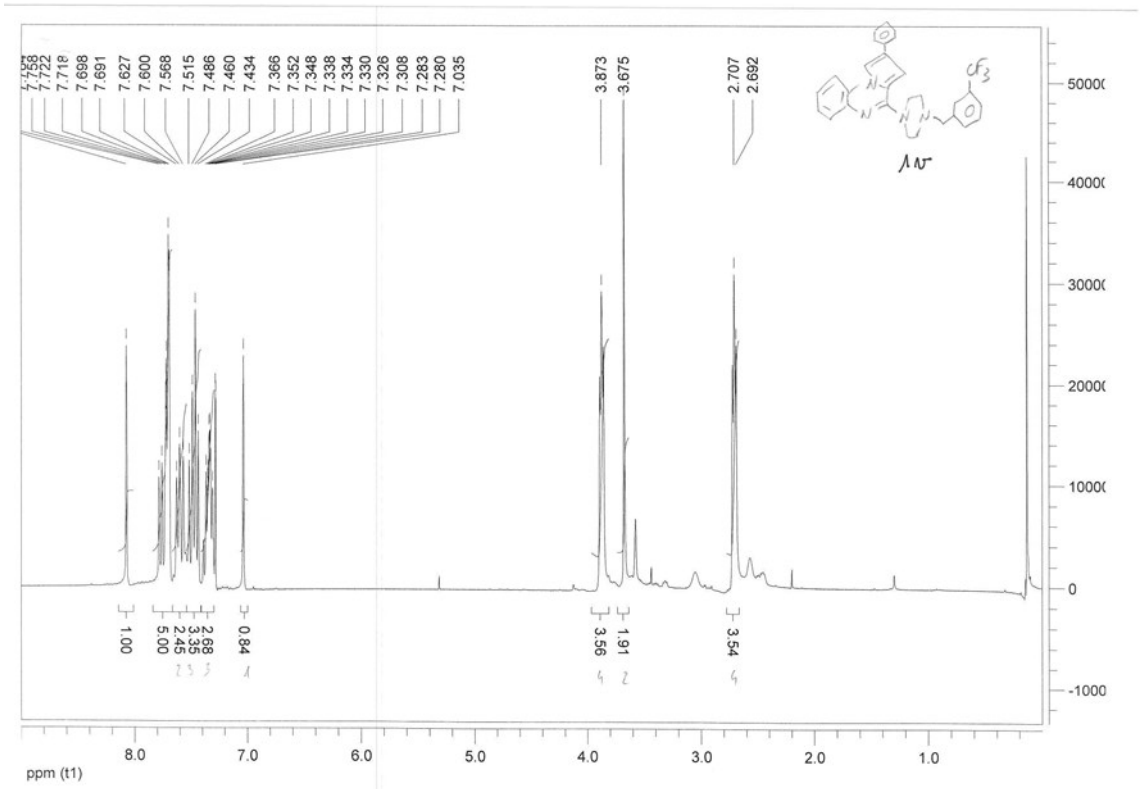

Fig. S42. ^{1}H NMR spectrum of **1v**.

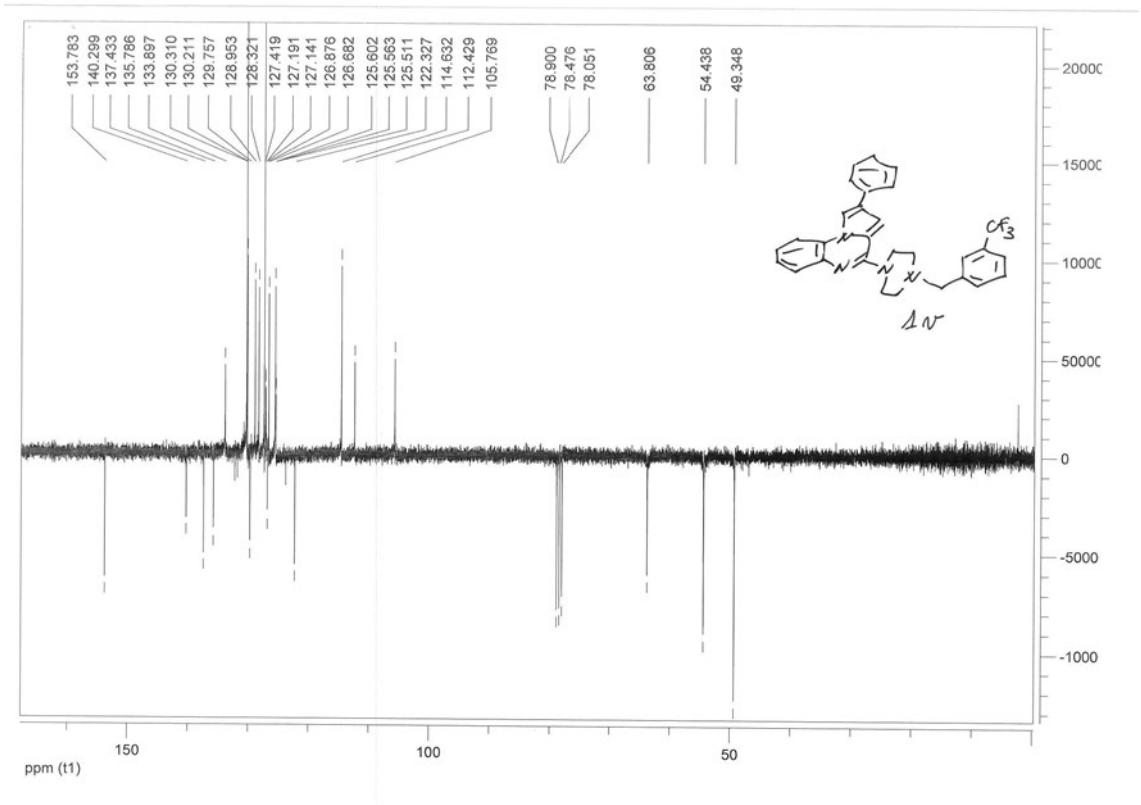

Fig. S43. ^{13}C NMR spectrum of **1v**.

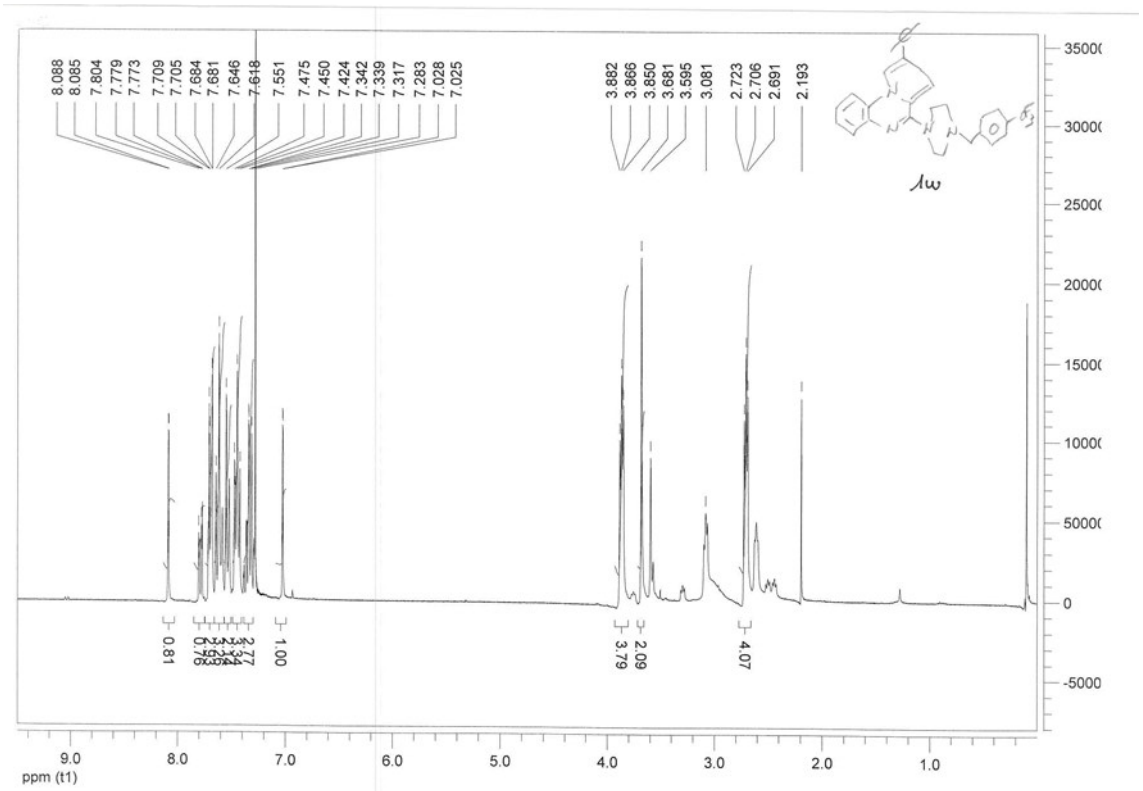

Fig.S44. ^{1}H NMR spectrum of **1w**.

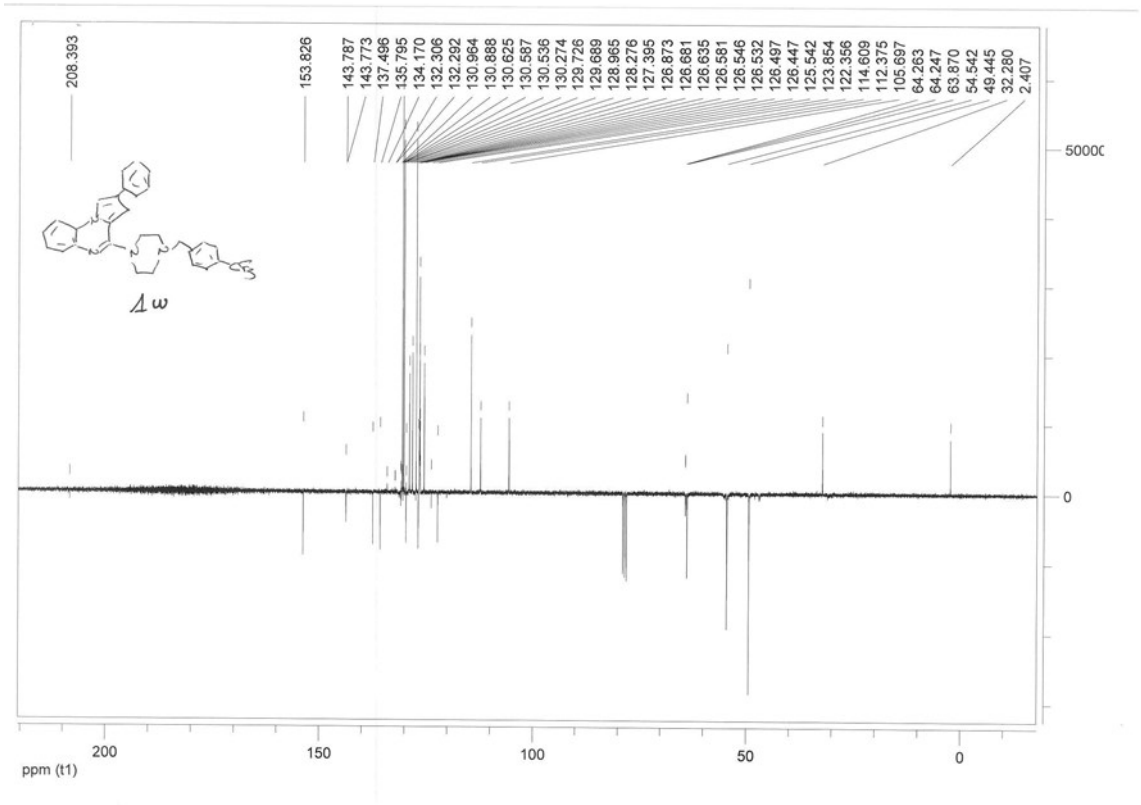

Fig. S45. ^{13}C NMR spectrum of **1w**.

Table S1. Intrinsic cytotoxicity of piperazinyl-pyrrolo[1,2-*a*]quinoxaline derivatives **1a-w** and **2a-f**.

Compounds	Yeast strains	[a]MIC_{80} (μM)	[b]RI
1a	AD1-8u^{-}	810±68	1
	CDR1	800±86	0.9
	MDR1	789±85	0.97
1b	AD1-8u^{-}	799±10	1
	CDR1	817±87	1.07
	MDR1	800±55	1.0

1c	AD1-8u^{-}	99±10	1
	CDR1	817±87	8.25
	MDR1	400±55	4.04
1d	AD1-8u^{-}	781±30	1
	CDR1	791±67	1.01
	MDR1	812±75	1.03
1e	AD1-8u^{-}	12±1.3	1
	CDR1	810±86	67.5
	MDR1	789±85	65.75
1f	AD1-8u^{-}	811±55	1
	CDR1	791±86	0.9
	MDR1	799±75	0.9
1g	AD1-8u^{-}	50±6	1
	CDR1	803±83	16
	MDR1	221±31	4.2
1h	AD1-8u^{-}	782±56	1
	CDR1	811±73	1.03
	MDR1	771±72	0.9
1i	AD1-8u^{-}	823±91	1
	CDR1	801±61	0.9
	MDR1	799±51	0.9
1j	AD1-8u^{-}	3±0.4	1
	CDR1	100±12	33.3
	MDR1	25±3	8.33
1k	AD1-8u^{-}	3±0.2	1
	CDR1	400±49	133.3
	MDR1	12±1	4
1l	AD1-8u^{-}	6±0.5	1
	CDR1	803±102	133.8
	MDR1	12±2	2
1m	AD1-8u^{-}	12±1.6	1
	CDR1	408±52	34
	MDR1	53±6.2	4.41
1n	AD1-8u^{-}	25±3.1	1
	CDR1	400±53	16

	MDR1	50±6.2	2
1o	AD1-8u^{-}	6±0.71	1
	CDR1	200±31	33.3
	MDR1	25±3.4	4.1
1p	AD1-8u^{-}	791±81	1
	CDR1	799±61	1.01
	MDR1	823±77	1.04
1q	AD1-8u^{-}	825±65	1
	CDR1	778±91	0.94
	MDR1	800±78	0.96
1r	AD1-8u^{-}	6±0.5	1
	CDR1	776±81	129.3
	MDR1	12±1.7	2
1s	AD1-8u^{-}	28±1.7	1
	CDR1	387±47	13.8
	MDR1	59±4.7	2.1
1t	AD1-8u^{-}	94±7.3	1
	CDR1	821±75	8.7
	MDR1	102±9.3	1.08
1u	AD1-8u^{-}	767±81	1
	CDR1	822±70	1.07
	MDR1	811±92	1.05
1v	AD1-8u^{-}	816±96	1
	CDR1	794±71	1.02
	MDR1	801±88	0.98
1w	AD1-8u^{-}	104±8.4	1
	CDR1	901±77	8.6
	MDR1	187±16	1.7
2a	AD1-8u^{-}	47±2.9	1
	CDR1	412±27	8
	MDR1	91±7.9	1.9
2b	AD1-8u^{-}	94±110	1
	CDR1	811±119	8.6
	MDR1	104±121	1.1
2c	AD1-8u^{-}	3±0.1	1

	CDR1	817±77	272.3
	MDR1	6±0.2	2
	AD1-8u^{-}	6±0.2	1
2d	CDR1	831±88	138.5
	MDR1	5±0.2	0.83
	AD1-8u^{-}	3±0.1	1
2e	CDR1	821±86	273.6
	MDR1	6±0.2	2
	AD1-8u^{-}	6±0.1	1
2f	CDR1	804±71	134
	MDR1	14±1.2	2.33

[a] The MIC_{80} values of cytotoxicity were determined by measuring the optical density of cultures of each strain in the absence and the presence of a range of concentrations of the different compounds. Yeast growth in the absence of inhibitor was considered as 100%, and the concentration where the growth was decreased to 80% was taken as MIC_{80}. The values are the means ± standard deviations of three independent experiments. [b] The resistance index (RI) was calculated as the ratio between the MIC_{80} values determined for the strain overexpressing the transporter relatively to that of the control strain (AD1-8u^{-}).

Table S2. Ability of piperazinyl-pyrrolo[1,2-*a*]quinoxaline derivatives to sensitize yeast growth to FLC cytotoxicity.

Strain	Compound	[a]FIC of fluconazole	[b]FIC of compound	[c]FICI
AD1-8u^{-}	**1a**	1 (1.5/1.5)	1 (810/810)	2 (1+1)
	1b	1 (1.5/1.5)	1 (799/799)	2 (1+1)
	1c	1 (1.5/1.5)	1 (99/99)	2 (1+1)
	1d	1 (1.5/1.5)	1 (781/781)	2 (1+1)
	1e	1 (1.5/1.5)	1 (12/12)	2 (1+1)
	1f	1 (1.5/1.5)	1 (811/811)	2 (1+1)
	1g	1 (1.5/1.5)	1 (50/50)	2 (1+1)
	1h	1 (1.5/1.5)	1 (782/782)	2 (1+1)
	1i	1 (1.5/1.5)	1 (823/823)	2 (1+1)
	1j	1 (1.5/1.5)	1 (3/3)	2 (1+1)
	1k	1 (1.5/1.5)	1 (3/3)	2 (1+1)
	1l	1 (1.5/1.5)	1 (6/6)	2 (1+1)
	1m	1 (1.5/1.5)	1 (12/12)	2 (1+1)
	1n	1 (1.5/1.5)	1 (25/25)	2 (1+1)

	1o	1 (1.5/1.5)	1 (6/6)	2 (1+1)
	1p	1 (1.5/1.5)	1 (791/791)	2 (1+1)
	1q	1 (1.5/1.5)	1 (825/825)	2 (1+1)
	1r	1 (1.5/1.5)	1 (6/6)	2 (1+1)
	1s	1 (1.5/1.5)	1 (28/28)	2 (1+1)
	1t	1 (1.5/1.5)	1 (94/94)	2 (1+1)
	1u	1 (1.5/1.5)	1 (767/767)	2 (1+1)
	1v	1 (1.5/1.5)	1 (816/816)	2 (1+1)
	1w	1 (1.5/1.5)	1 (104/104)	2 (1+1)
	2a	1 (1.5/1.5)	1 (47/47)	2 (1+1)
	2b	1 (1.5/1.5)	1 (94/94)	2 (1+1)
	2c	1 (1.5/1.5)	1 (3/3)	2 (1+1)
	2d	1 (1.5/1.5)	1 (6/6)	2 (1+1)
	2e	1 (1.5/1.5)	1 (3/3)	2 (1+1)
	2f	1 (1.5/1.5)	1 (6/6)	2 (1+1)
AD1-CDR1	**1a**	0.7 (163/209)	1 (800/800)	1.7 (0.7+1)
	1b	0.7 (163/209)	1 (817/817)	1.7 (0.7+1)
	1c	0.3 (81/209)	1 (817/817)	1.3 (0.3+1)
	1d	0.3 (81/209)	1 (791/791)	1.3 (0.3+1)
	1e	0.7 (167/209)	1 (810/810)	1.7 (0.7+1)
	1f	0.1 (40/209)	1 (791/791)	1.1 (0.1+1)
	1g	0.3 (81/209)	1 (803/803)	1.3 (0.3+1)
	1h	0.7 (163/209)	1 (811/811)	1.7 (0.7+1)
	1i	0.7 (163/209)	1 (801/801)	1.7 (0.7+1)
	1j	0.09 (20/209)	1 (100/100)	1.09 (0.09+1)
	1k	0.7 (163/209)	1 (400/400)	1.7 (0.7+1)
	1l	0.3 (81/209)	1 (803/803)	1.3 (0.3+1)
	1m	0.1 (40/209)	1 (408/408)	1.1 (0.1+1)
	1n	0.7 (163/209)	1 (400/400)	1.7 (0.7+1)
	1o	0.7 (163/209)	1 (200/200)	1.7 (0.7+1)
	1p	0.3 (81/209)	1 (799/799)	1.3 (0.3+1)
	1q	0.7 (167/209)	1 (778/778)	1.7 (0.7+1)
	1r	0.3 (81/209)	1 (776/776)	1.3 (0.3+1)
	1s	0.7 (163/209)	1 (387/387)	1.7 (0.7+1)
	1t	0.3 (81/209)	1 (821/821)	1.3 (0.3+1)
	1u	0.1 (40/209)	1 (822/822)	1.1 (0.1+1)
	1v	0.7 (163/209)	1 (794/794)	1.7 (0.7+1)
	1w	0.1 (40/209)	1 (901/901)	1.1 (0.1+1)

	2a	0.3 (81/209)	1 (412/412)	1.3 (0.3+1)
	2b	0.7 (163/209)	1 (811/811)	1.7 (0.7+1)
	2c	0.7 (163/209)	1 (817/817)	1.7 (0.7+1)
	2d	0.09 (20/209)	1 (831/841)	1.09 (0.09+1)
	2e	0.7 (163/209)	1 (821/821)	1.7 (0.7+1)
	2f	0.1 (40/209)	1 (804/804)	1.1 (0.1+1)
AD1-MDR1	**1a**	0.6 (40/65)	1 (789/789)	1.6 (0.6+1)
	1b	0.3 (20/65)	1 (800/800)	1.3 (0.3+1)
	1c	0.3 (20/65)	1 (400/400)	1.3 (0.3+1)
	1d	0.15 (10/65)	0.0076 (6.25/812)	0.15
	1e	0.6 (40/65)	1 (789/789)	1.6 (0.6+1)
	1f	0.15 (10/65)	0.25 (200/799)	0.4 (0.15+0.25)
	1g	0.6 (40/65)	1 (221/221)	1.6 (0.6+1)
	1h	0.6 (40/65)	1 (771/771)	1.6 (0.6 +1)
	1i	0.6 (40/65)	1 (799/799)	1.6 (0.6+1)
	1j	0.6 (40/65)	1 (25/25)	1.6 (0.6+1)
	1k	0.6 (40/65)	1 (12/12)	1.6 (0.6+1)
	1l	0.6 (40/65)	1 (12/12)	1.6 (0.6+1)
	1m	0.6 (40/65)	1 (53/53)	1.6 (0.6 +1)
	1n	0.6 (40/65)	1 (50/50)	1.6 (0.6+1)
	1o	0.3 (20/65)	1 (25/25)	1.3 (0.3+1)
	1p	0.3 (20/65)	1 (823/823)	1.3 (0.3+1)
	1q	0.6 (40/65)	1 (800/800)	1.6 (0.6+1)
	1r	0.6 (40/65)	1 (12/12)	1.6 (0.6+1)
	1s	0.3 (20/65)	1 (59/59)	1.3 (0.3+1)
	1t	0.3 (20/65)	1 (102/102)	1.3 (0.3+1)
	1u	0.3 (20/65)	1 (811/811)	1.3 (0.3+1)
	1v	0.6 (40/65)	1 (801/801)	1.6 (0.6 +1)
	1w	0.6 (40/65)	1 (187/187)	1.6 (0.6+1)
	2a	0.3 (20/65)	1 (91/91)	1.3 (0.3+1)
	2b	0.3 (20/65)	1 (104/104)	1.3 (0.3+1)
	2c	0.6 (40/65)	1 (6/6)	1.6 (0.6+1)
	2d	0.6 (40/65)	1 (5/5)	1.6 (0.6+1)
	2e	0.3 (20/65)	1 (6/6)	1.3 (0.3+1)
	2f	0.3 (20/65)	1 (14/14)	1.3 (0.3+1)
F2	**1d**	1 (13/13)	1 (618/618)	2 (1+1)
	1f	0.5 (7.5/13)	1 (400/400)	1.5 (0.5+1)
F5	**1d**	0.4 (200/418)	0.2 (150/720)	0.6 (0.2+0.4)
	1f	0.35 (150/418)	0.43 (350/799)	0.78 (0.35+0.43)

[a] Evaluated by the checkerboard method, and expressed as the fractional inhibitory concentration (FIC) values for the fluconazole (= MIC_{80} of fluconazole in combination/MIC_{80} of fluconazole alone) and [b] each compound (= MIC_{80} of compound in combination/MIC_{80} of compound alone). The values in brackets are expressed in μM. [c] FIC index (FICI) value ≤ 0.5 indicates synergistic interaction between the compound and the fluconazole.